SYNTHETIC STUDIES WITH THE HEXAHYDROFLUORENONE SYSTEM

A THESIS

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By

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SYNTHETIC STUDIES WITH THE HEXAHYDROFLUORENONE SYSTEM

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I want to thank my parents for their continuous support throughout my education, to them this thesis is dedicated.

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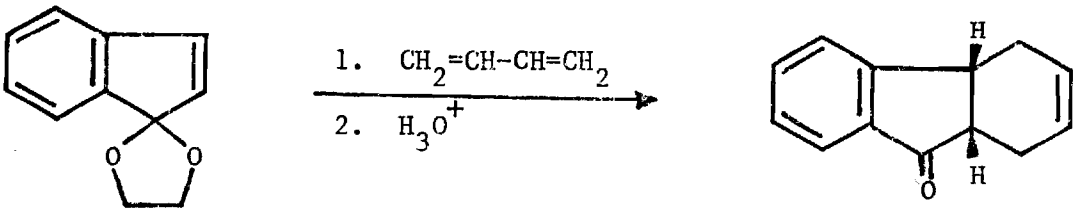
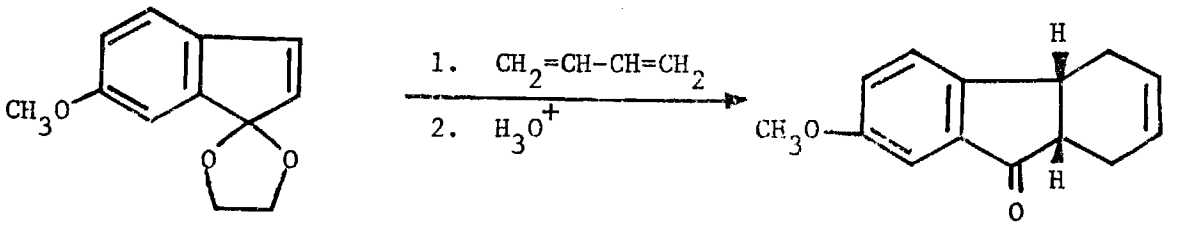
Several different approaches to the preparation of gibberellins and related molecules are surveyed.

Chapter II THE USE OF INDENONE ETHYLENE KETALS AS DIENOPHILES

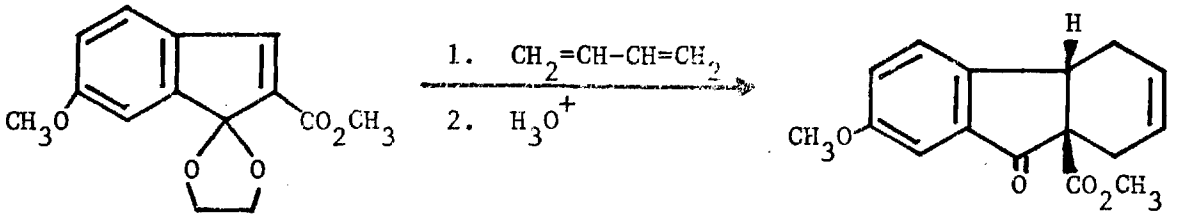
Synthetic routes for the preparation of indenone ethylene ketals 1, 3, and 5, have been studied. Reaction of these dienophiles with butadiene followed by hydrolysis yielded ketones 2, 4, and 6. These molecules are of synthetic interest as intermediates for the preparation of gibberellins.



1 2



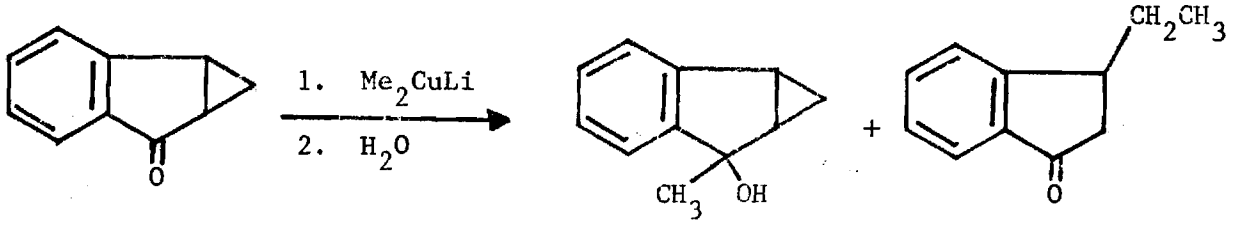
3 4



5 6

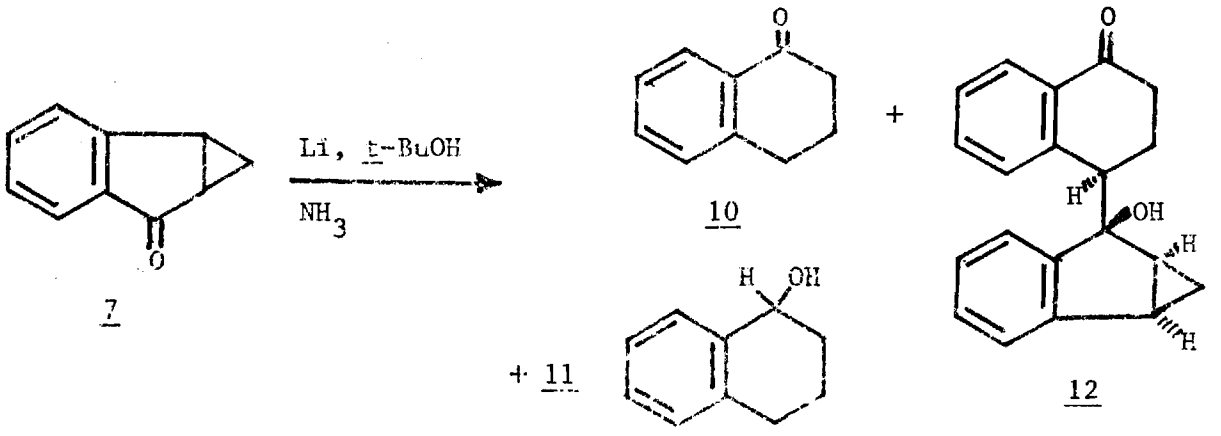
Chapter III OPENING OF A CYCLOPROPYL KETONE THAT IS PART OF AN INDANONE SYSTEM

The reaction of cyclopropyl ketone 7 with Me_2CuLi was studied and found to yield as major products alcohol 8 and ketone 9. Evidence is presented indicating that the reaction occurs by an S_N2 attack by the cuprate reagent rather than by an initial electron transfer step.



7 8 9

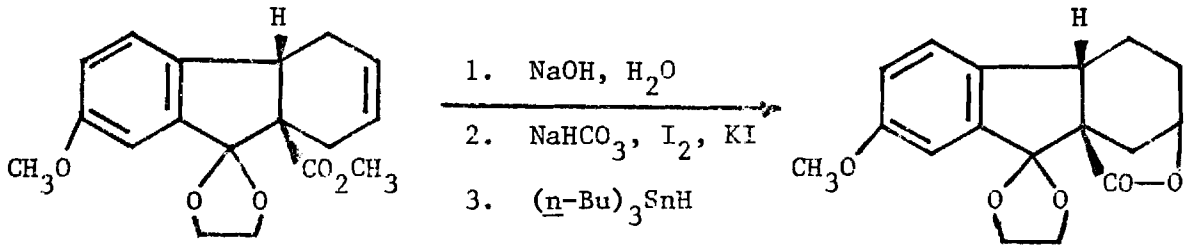
To compare the products obtained from a known electron transfer reaction, ketone 7 was reduced with Li and t-butyl alcohol in liquid ammonia and products 10, 11, and 12 were isolated.



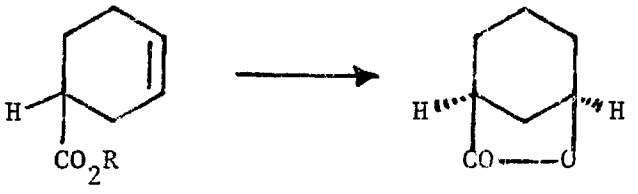
7 10 + 11 12

Chapter IV STUDIES ON THE SYNTHESIS OF GAMMA-LACTONES

Lactone 14 was prepared from ester 13 as a potential gibberellin intermediate. Methods to convert the model systems 15 and 16 into gamma-lactone 17 were investigated.



13 14



15, R = H
16, R = CH_3

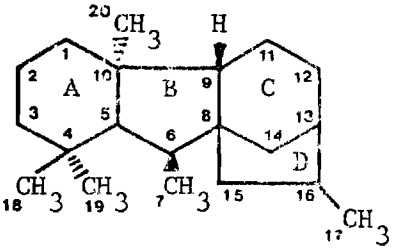
17

CHAPTER I

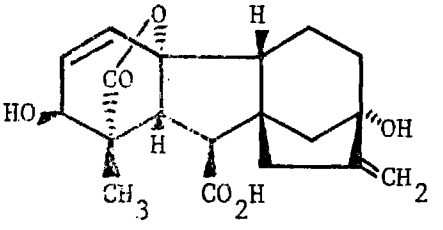
SURVEY OF SYNTHETIC APPROACHES TO THE B-C-D RING OF GIBBERELLINS

The gibberellins are a group of naturally occuring tetracyclic compounds that function as plant growth hormones.[1] The compounds were first isolated from metabolism of the fungi Gibberella fujikuroi and later from higher plants. To date, 50 different gibberellins have been isolated and their structures elucidated. The gibberellins have in common a structure based upon the ent-gibberellane skeleton 1.

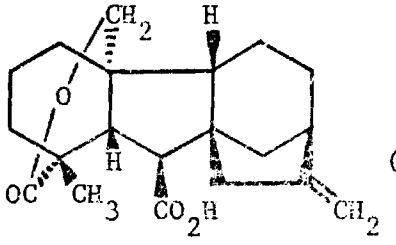
The gibberellins are divided into the C-20 and C-19 gibberellins where the C-19 gibberellins have lost the carbon atom (C-20 of structure 1) at C-10. The first gibberellin to be isolated as a crystalline substance was gibberellin A_3 (GA_3) known also as gibberellic acid (2). The first gibberellins of each type to be synthesized were gibberellin A_{15}[2] (3), a C-20 gibberllin, and gibberellin A_4[3] (4), a C-19 molecule.



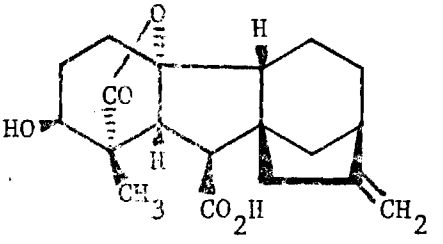
1



2 (GA_3)



3 (GA_{15})



4 (GA_4)

To date, many gibberellins have been synthesized through a variety of approaches, and a great deal of additional work has been reported regarding preparation of synthetically useful intermediates. This chapter will survey some of the methods used in preparing the B-C-D ring system of gibberellins and related molecules.

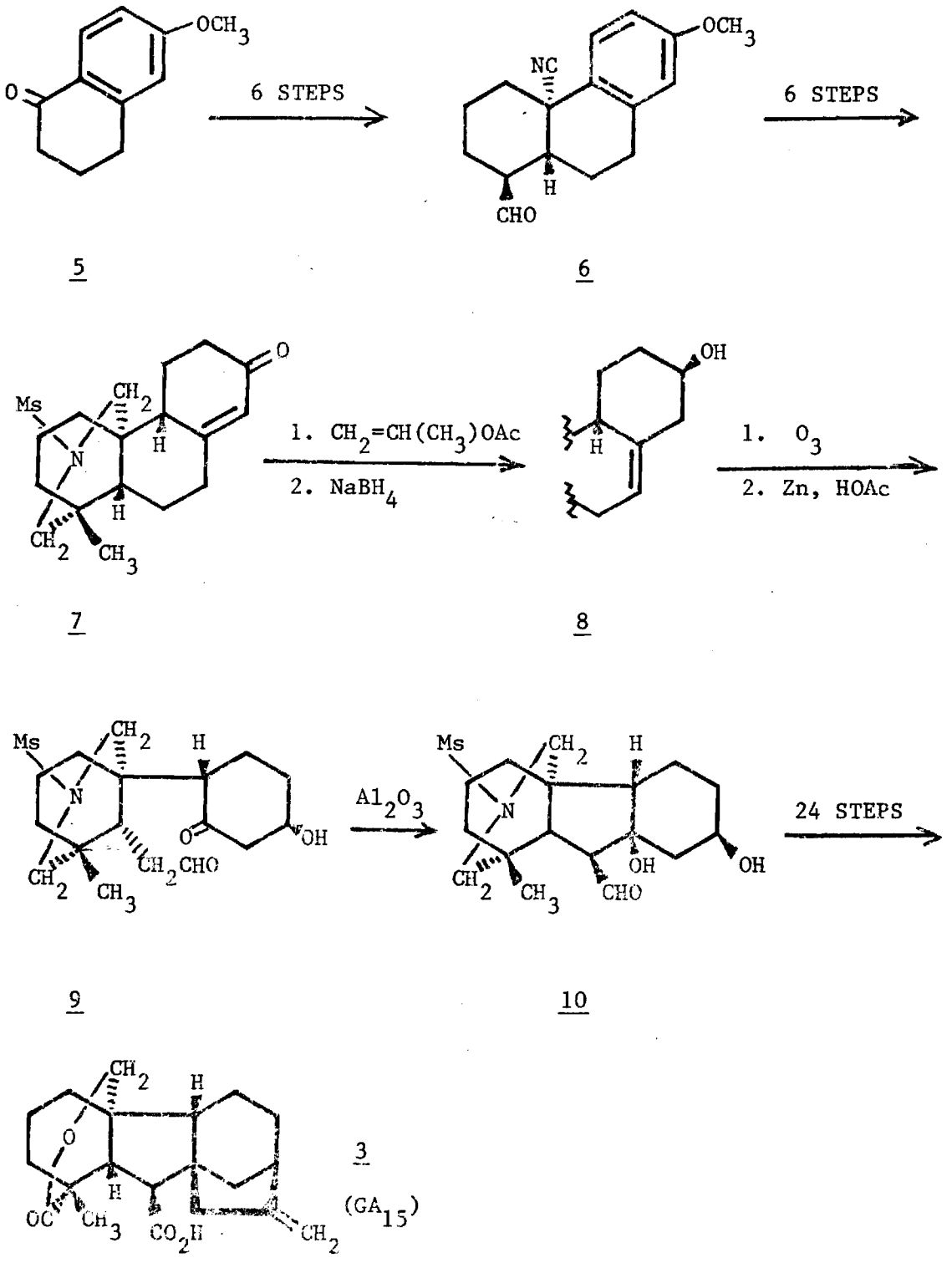
The tetracyclic ring system of the gibberellins can be constructed through a variety of approaches. The methods can be generally divided into three groups. The first group involves the sequential construction of one ring system after another while the second group involves separate preparation of two or more ring systems which are then coupled and further elaborated. The third group involves modifying naturally occurring molecules to form the gibberellin skeleton.

C-20 Gibberellins

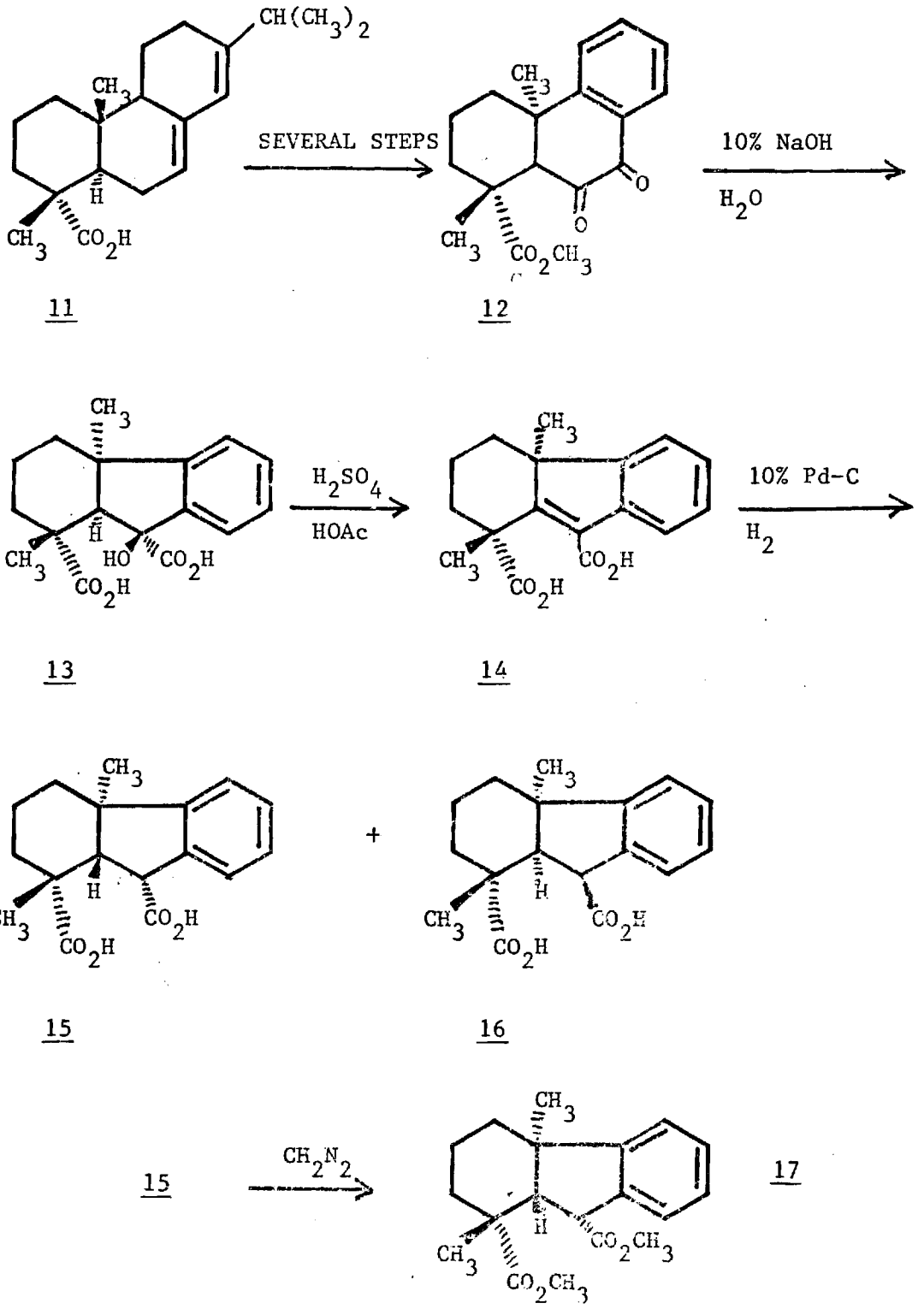
A rather involved synthesis of the C-20 gibberellin A_{15} by Nagata[2] (Scheme I) exemplifies a method whereby the B ring is initially prepared as a 6 membered ring that is then contracted to yield a functionalized 5-membered B ring. To prepare the B ring, alkene 8 was treated with ozone followed by reduction with zinc and acetic acid to yield ketoaldehyde 9. An aldol condensation was brought about by treating 9 with alumina to yield aldehyde 10 containing a functionalized B ring. An additional 24 steps culminated in the preparation of gibberellin A_{15} (3).

A different approach to C-20 gibberellins utilized a naturally occurring molecule as the starting material. An example is Tahara's[4] synthesis of gibberellin A_{12} (Scheme II), from l-abietic acid (11), a major component of pine rosin. The dioxo ester 12 was prepared in

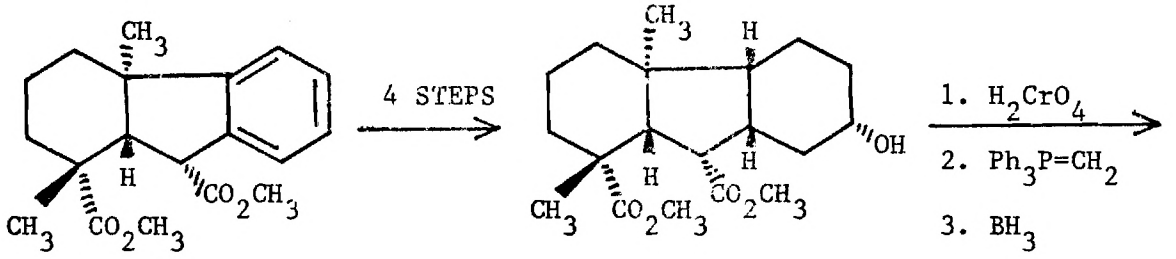
SCHEME I


OCH3
O
6 STEPS
NC
OCH3
H
CHO
6 STEPS
5
6
Ms
CH2
N
H
O
H
CH2
CH3
1. CH2=CH(CH3)OAc
2. NaBH4
OH
H
1. O3
2. Zn, HOAc
7
8
Ms
CH2
H
N
O
OH
CH2
CH2CHO
CH3
Al2O3
Ms
CH2
H
N
OH
OH
CH2
CH3
CHO
24 STEPS
9
10
CH2
H
O
H
OC
CH3
CO2H
CH2
3
(GA15)

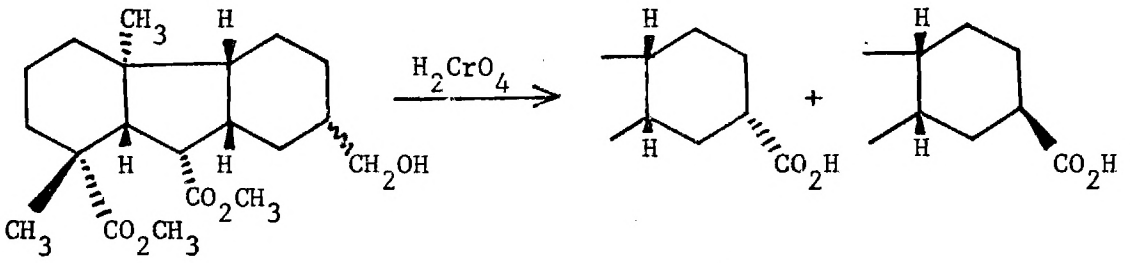
SCHEME II


CH(CH3)2
CH3
H
CH3
CO2H
SEVERAL STEPS
CH3
O
O
CH3
CO2CH3
10% NaOH
H2O
11
12
CH3
H
CH3
HO
CO2H
CO2H
H2SO4
HOAc
CH3
CH3
CO2H
CO2H
10% Pd-C
H2
13
14
CH3
H
CH3
CO2H
CO2H
+
CH3
H
CH3
CO2H
CO2H
15
16
15
CH2N2
CH3
H
CH3
CO2CH3
CO2CH3
17

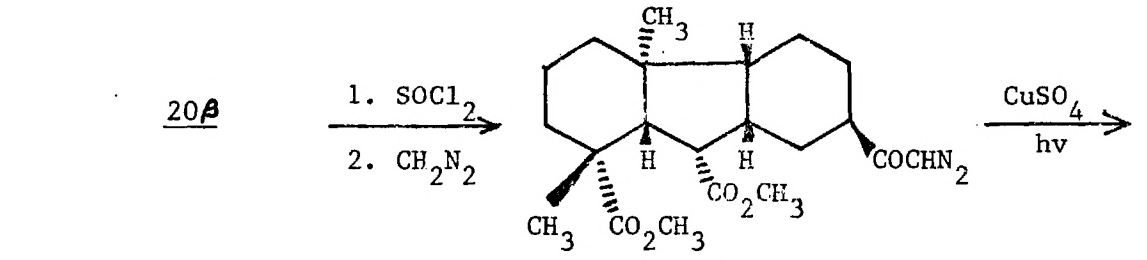
SCHEME II (CONTINUED)



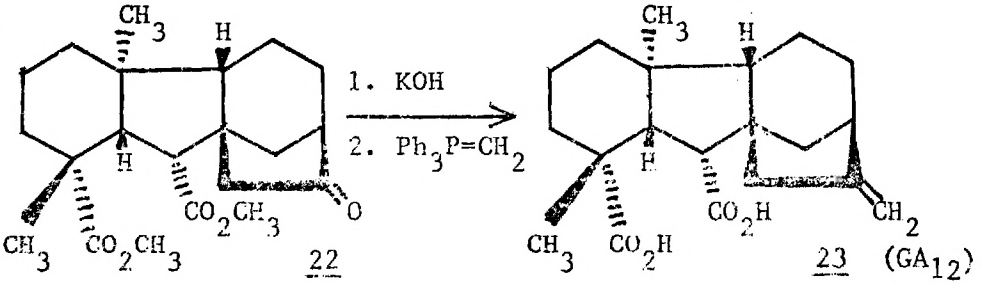
17 18



19 20α 20β



21



22 23 (GA_{12})

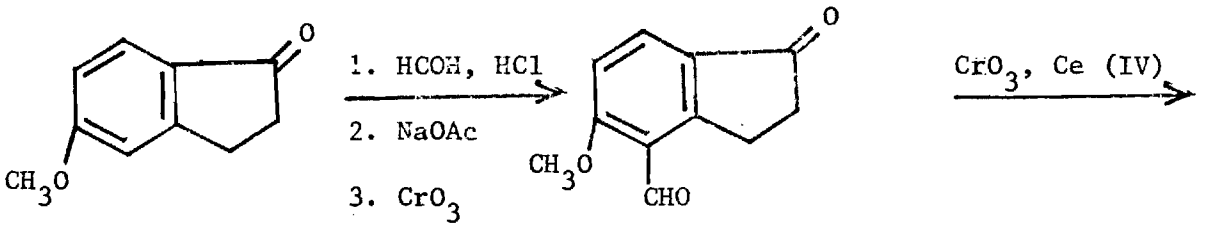
several steps from l-abietic acid (11) with the net formation of a cis A-B ring from a trans A-B ring. Treatment of 12 with boiling 10% aqueous NaOH afforded on benzilic acid rearrangement the diacid 13 containing an A-B cis-hexahydrofluorene system. Further transformation yielded a mixture of diacids 15 and 16 that were separated[4b] through multiple crystallizations and chromatography. Ten additional steps culminated in an intramolecular carbene insertion of 21 to produce the D ring containing diester 22 which was directly convertible into gibberellin A_{12} (23).

C-19 Gibberellins

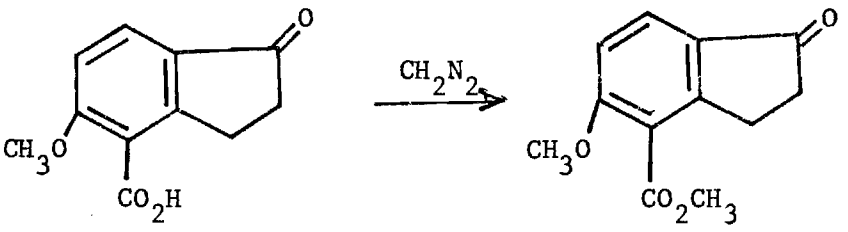
An example of the stepwise construction of the gibberellin skeleton is Loewenthal's[5] synthesis of an intermediate useful in the total synthesis of gibberellin A_4 (Scheme III). Starting with either 5-methoxy-1-indanone or 7-methoxy-1-indanone (24 or 28) the intermediate keto ester 27 was prepared followed by condensation, hydrogenation, and then methanolysis to yield keto diester 30. Reaction of 30 with methyl vinyl ketone formed the product 31 containing the A, B, and C rings. Cyclization of carboxylic acid 31 with a mixture of trifluoroacetic acid and trifluoroacetic anhydride yielded diketone 32. Hydrogenation with Pd on carbon in acetic acid yielded ketone 33 which was further transformed into gibberellin intermediate 35. Of note is the trans stereochemistry of the hydrogen at C-4a of diester 35 relative to the D ring since the gibberellins possess a cis stereochemistry at that carbon.

A second example that also yields a trans stereochemistry at C-4a is the preparation of ketone 42a by Ghatak[6] (Scheme IV). In this

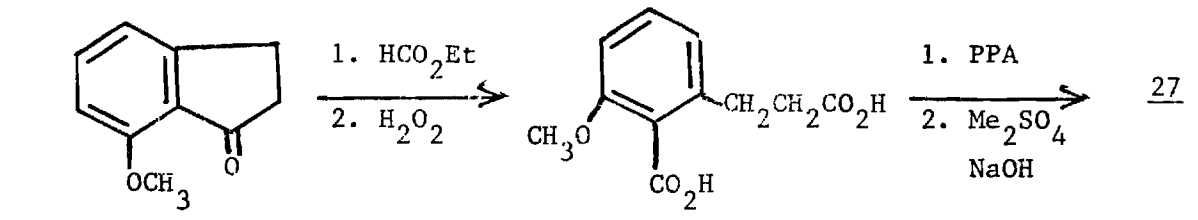
SCHEME III



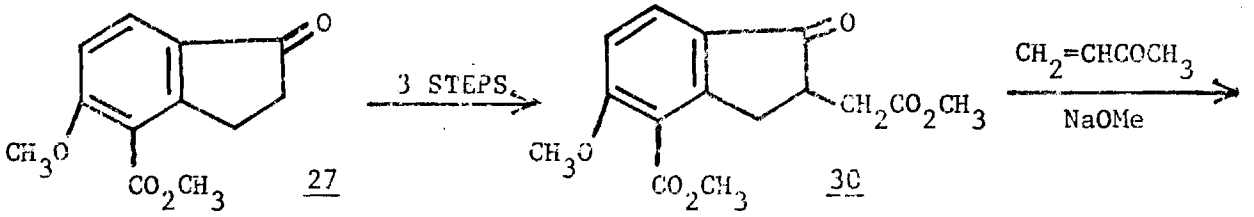
24 25



26 27

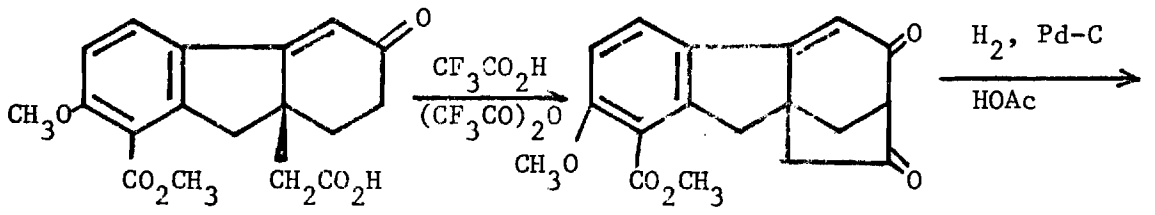


28 29

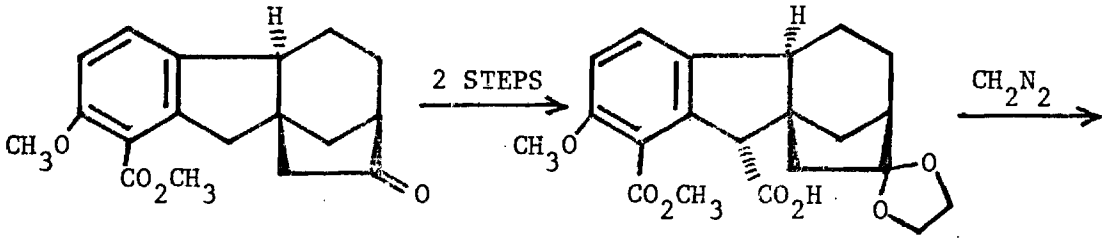


27 30

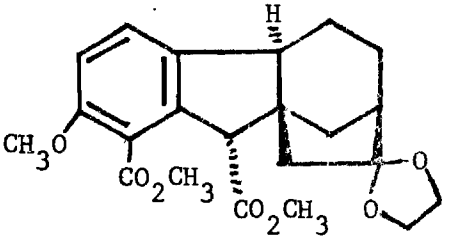
SCHEME III (CONTINUED)



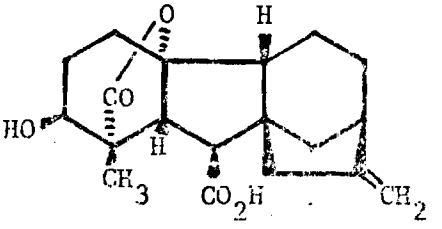
31 32



33 34

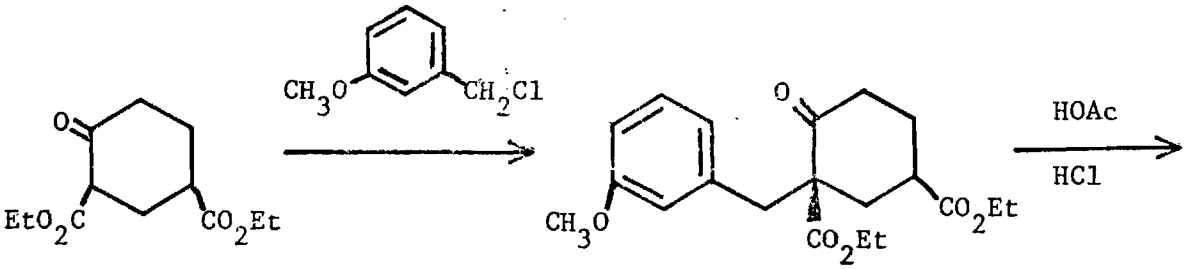


35

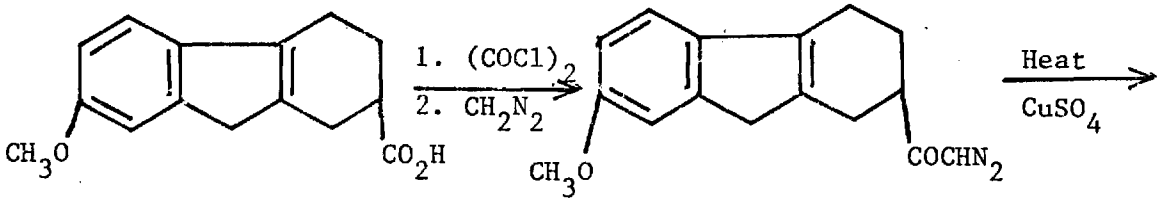


4 (GA_4)

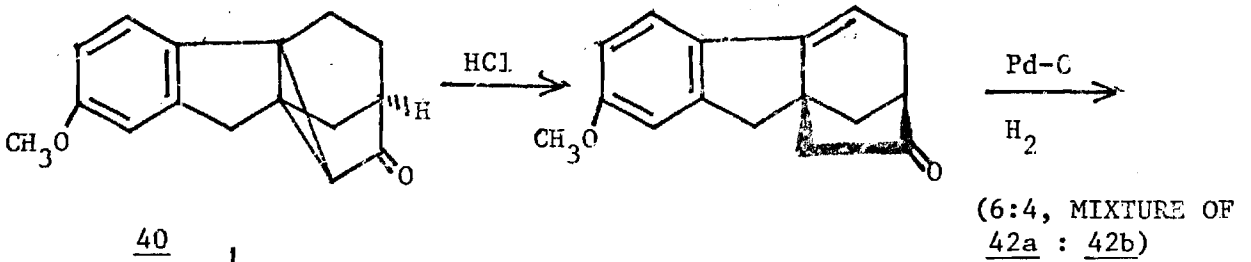
SCHEME IV



36 37



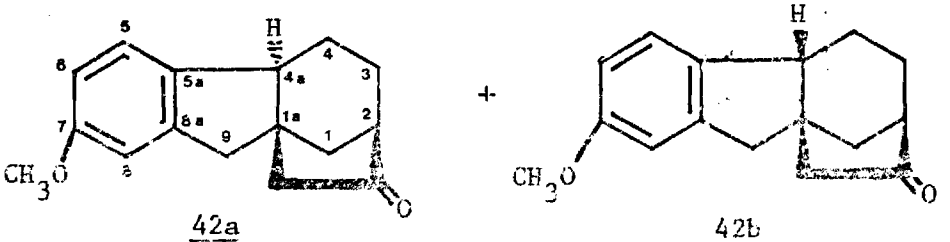
38 39



40 41

(6:4, MIXTURE OF 42a : 42b)

Pd-C
H_2
(100% 42a)



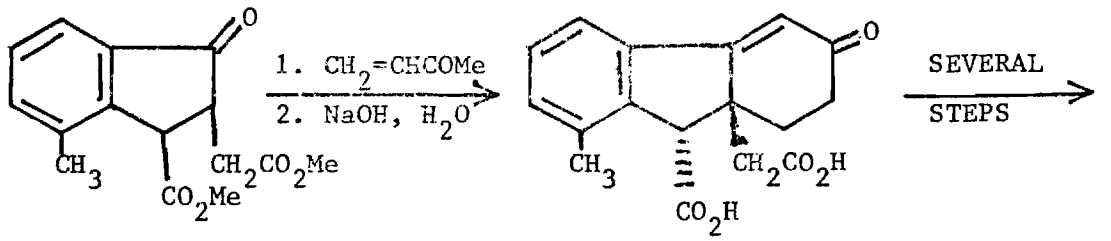
42a 42b

sequence the authors independently constructed the A and C ring systems followed by coupling them to yield keto diester 37. An acid-catalyzed ring closure and decarboxylation then yielded carboxylic acid 38. The D ring was then constructed through an interesting although preparatively disappointing sequence. The acid chloride of 38 was prepared with oxalyl chloride followed by reaction with diazomethane to yield diazo ketone 39. The copper sulfate-catalyzed addition of the diazo ketone to the double bond yielded the cyclopropyl ketone 40 in 24% overall yield from 38. Treatment of 40 with HCl in chloroform yielded the rearranged ketone 41 that was then hydrogenated to yield ketones 42a and 42b. The cyclopropylketone 40 could also be hydrogenated directly to yield ketone 42a.

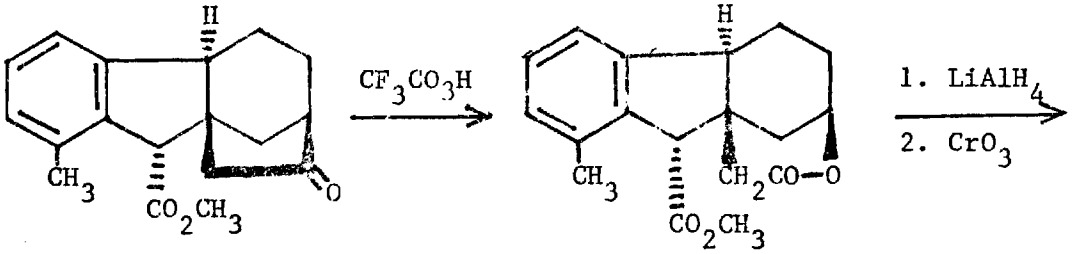
Mori has shown[7] that compounds with trans-B,C rings (ie., compounds 35 Scheme III and 42a Scheme IV) can be readily transformed into the correctly functionalized B-C-D ring system of many gibberellins (Scheme V). Keto ester 45 was prepared in several steps from compound 43 followed by peracid oxidation to yield ketone 46. Several additional steps yielded keto acid 49 that was then cyclized to yield diketone 50. This diketone (50) was then transformed in one step through a reductive rearrangement to yield keto alcohols 51a and 51b. Reaction of 51a with $(Ph)_3P=CH_2$ followed by hydrolysis of the ester yielded epiallogibberic acid 52.

An approach that generated the correct cis stereochemistry for the C-D rings is that of Ziegler[8] (Scheme VI). The A and C rings were combined in the preparation of compound 54 followed by dehydration to yield enone 55. Hydrogenation of enone 55 followed by polyphosphoric acid

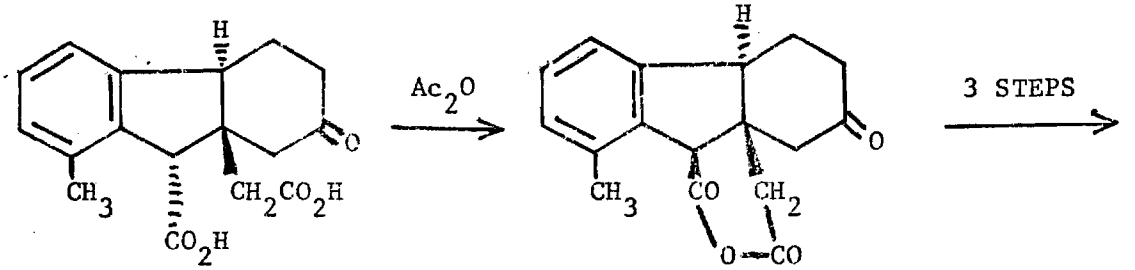
SCHEME V



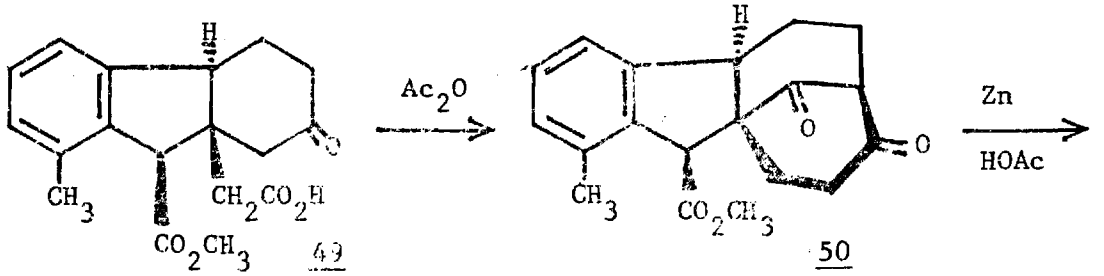
43 44



45 46

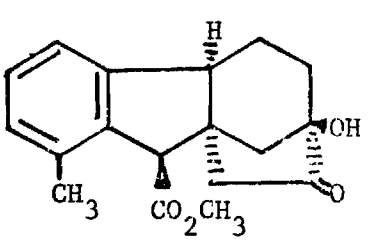


47 48



49 50

SCHEME V (CONTINUED)



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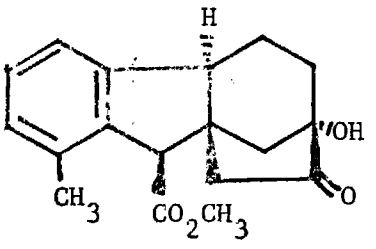
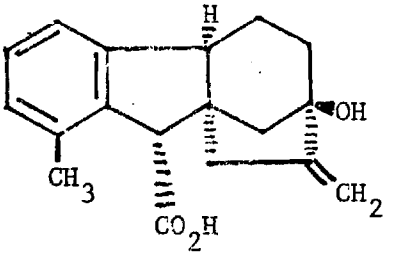


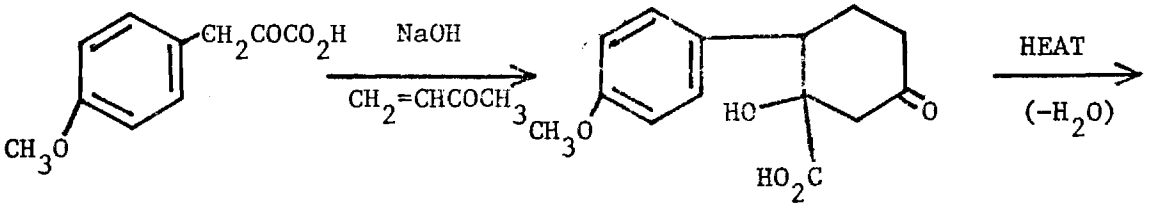
51a 51b

51a $\xrightarrow[2.\ NaOH]{1.\ Ph_3P{=}CH_2}$

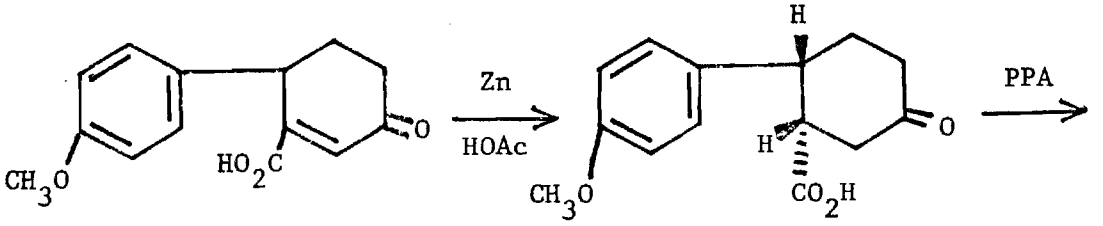


52

SCHEME VI



53 54



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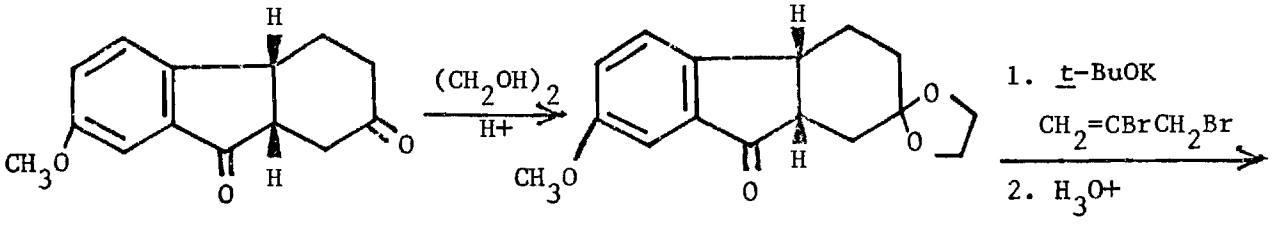
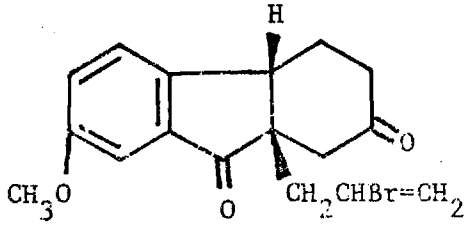
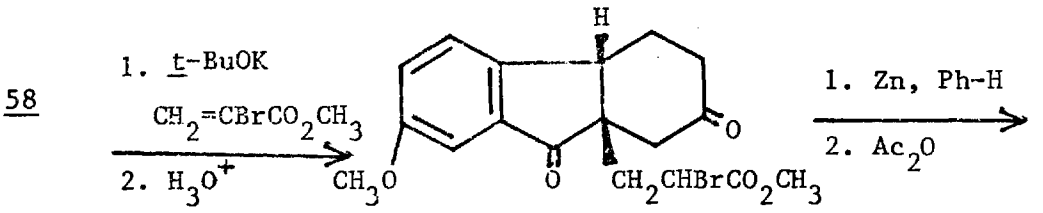


57 58

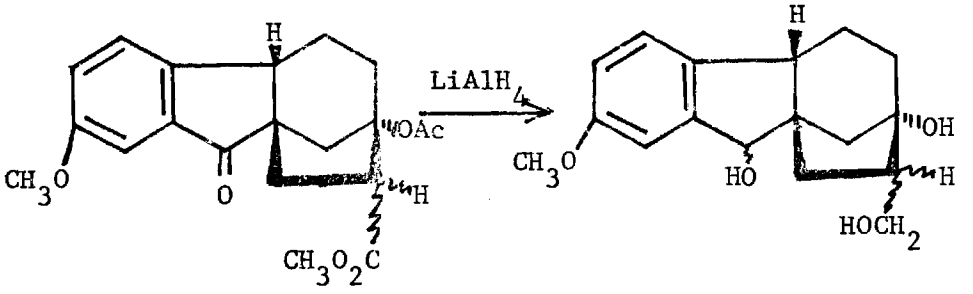


59

SCHEME VI (CONTINUED)



60



61 62

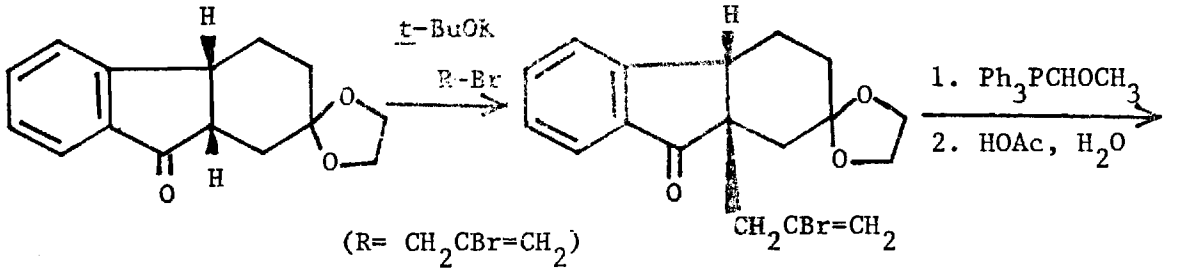
cyclization formed diketone 57 which was then selectively ketalized to form 58. The stereochemistry of the B-C rings was then established by alkylation at the bridgehead carbon with KOBu-t and 2,3-dibromopropene followed by hydrolysis of the ketal to yield bromoketone 59. Alternatively the ketal 58 was alkylated with methyl α-bromoacrylate followed by hydrolysis of the ketal to yield bromoester 60. The D ring was then constructed by treating the bromoester with zinc in refluxing benzene. Subsequent transformation yielded triol 62.

The work of Corey[9] (Scheme VII) has shown that vinyl bromoketones of the type 64 can be transformed into compounds containing the functionalized C-D ring in three steps.

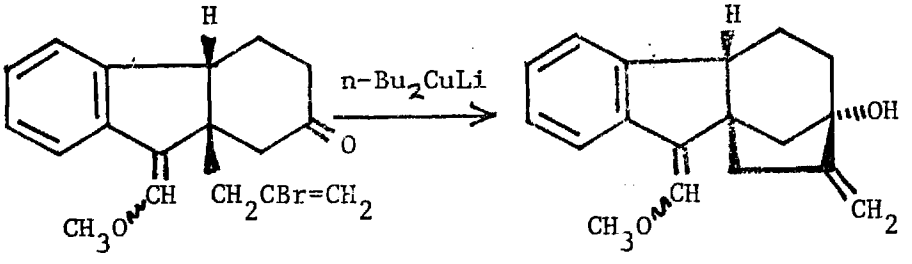
A procedure that constructs the B ring system last is that of Baker[10] (Scheme VIII). The A and C rings were combined in the preparation of compound 69 followed by addition of the D ring to form compound 72. Treatment of 72 with thionyl chloride followed by $AlCl_3$ in CH_2Cl_2 yielded compound 73 in 90% yield. In an additional series of steps[10b] compound 73 was converted into gibberellin intermediates 75 and 76.

House[11a] utilized the Diels-Alder reaction to generate the cis stereochemistry of the C ring in his preparation of gibberellin intermediates (Scheme IX). The starting ketone 77 was prepared in six steps in 61% yield[11b] from anisaldehyde. Subsequent steps yielded diester 80 in 50% yield from 77. The ester was then equilibrated with base to yield the desired dienophile 81. Reaction with butadiene yielded a mixture of the desired ester 82 and a byproduct ester 83 in 32% and 26% isolated yield respectively. The byproduct ester 83 was formed from reaction of butadiene with ester 80 which arose from isomerization of

SCHEME VII

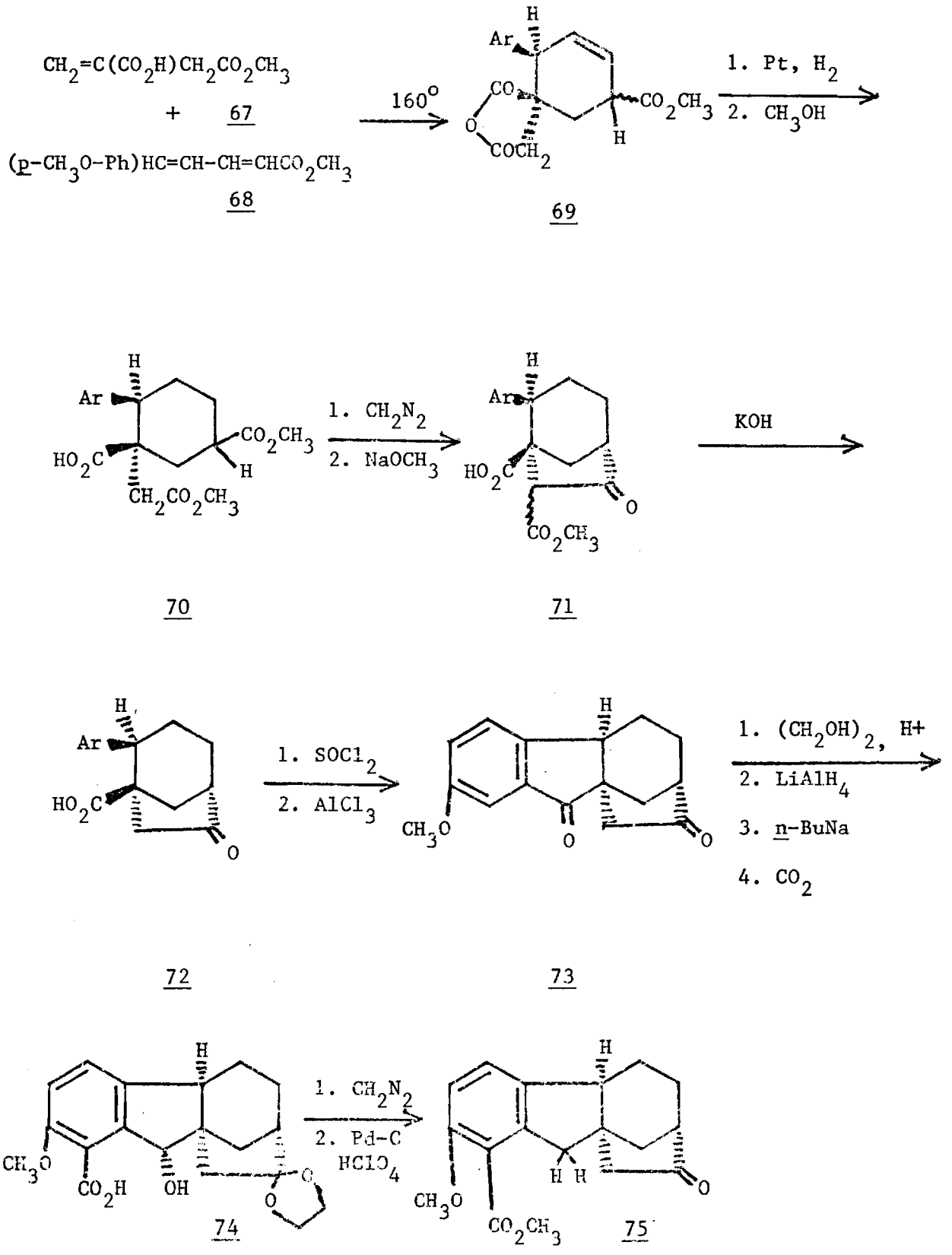


63 64

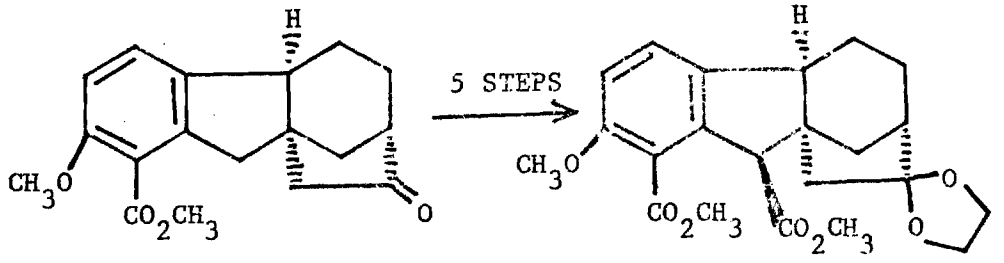


65 66

SCHEME VIII

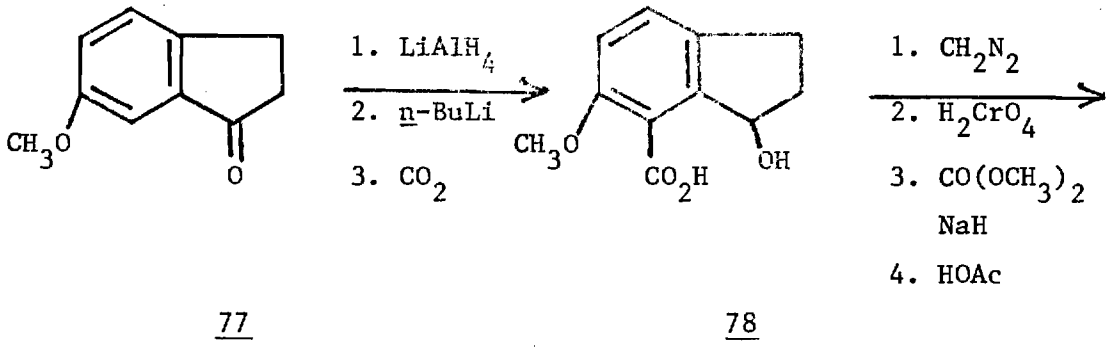

CH2=C(CO2H)CH2CO2CH3
+ 67
(p-CH3O-Ph)HC=CH-CH=CHCO2CH3
68
160°
69
1. Pt, H2
2. CH3OH
70
1. CH2N2
2. NaOCH3
71
KOH
72
1. SOCl2
2. AlCl3
73
1. (CH2OH)2, H+
2. LiAlH4
3. n-BuNa
4. CO2
74
1. CH2N2
2. Pd-C
HClO4
75

SCHEME VIII (CONTINUED)

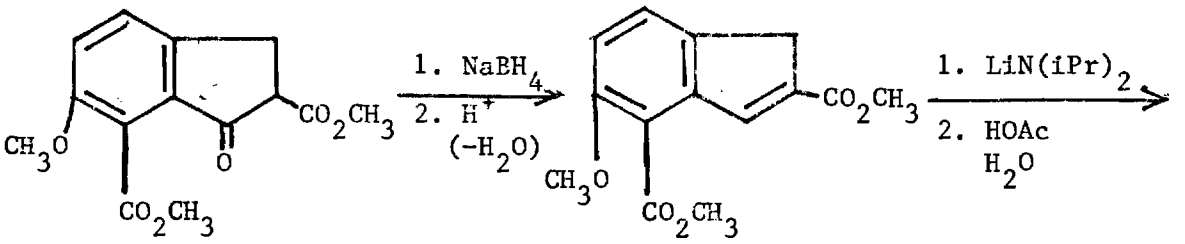


75 76

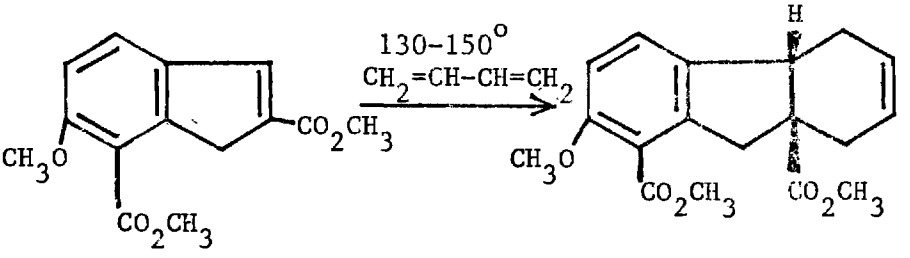
SCHEME IX



77 78

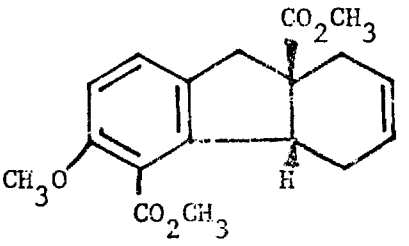


79 80



81 82 (32%)

+



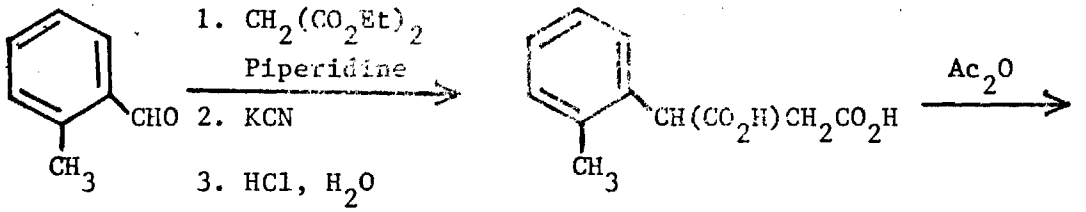
83 (26%)

ester 81 under the strenuous reaction conditions.

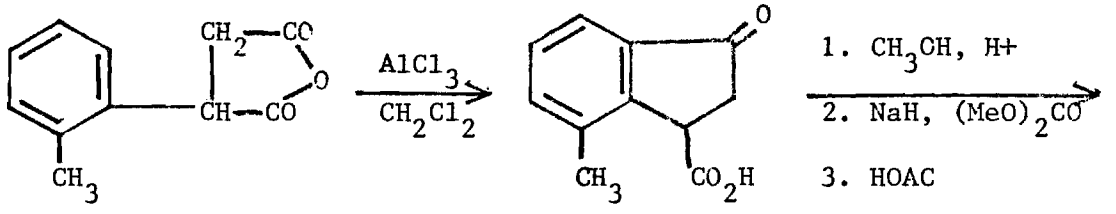
A similar sequence, also by House,[12a] is shown in Scheme X. Dienophile diester 89 was prepared through a series of steps from O-tolualdehyde and was then allowed to react with butadiene to generate ester 90 in 31% yield. Unfortunately reaction[12b] of methoxy ester 91 (prepared through a method essentially the same as that used to prepare 89 although starting with m-methoxy benzaldehyde) with butadiene yielded only product ester 92 derived from isomerization of the double bond of 91 followed by reaction with butadiene and none of the desired 93 was isolated.

Greater success was obtained by Martens[13] when he used the Diels-Alder reaction to prepare the C ring in his preparation of gibberellin like compounds (Scheme XI). Reaction of dienophile 99 with butadiene yielded the product alkene 100 in 93% yield. The synthesis was then concluded by transforming ester 100 into a system containing the A-B-C-D ring system with the correct stereochemistry.

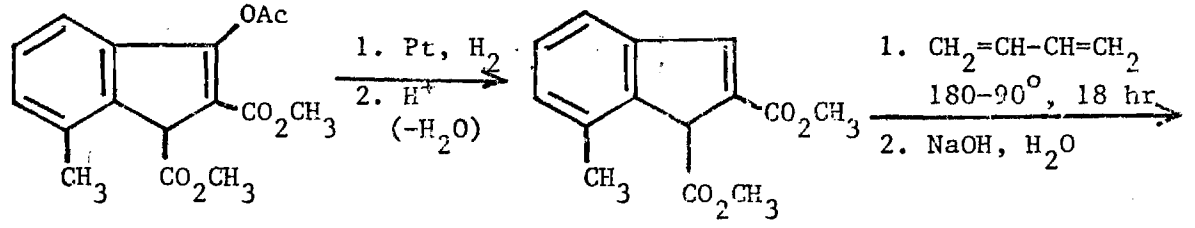
SCHEME X



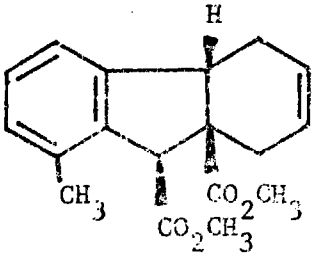
84 85



86 87

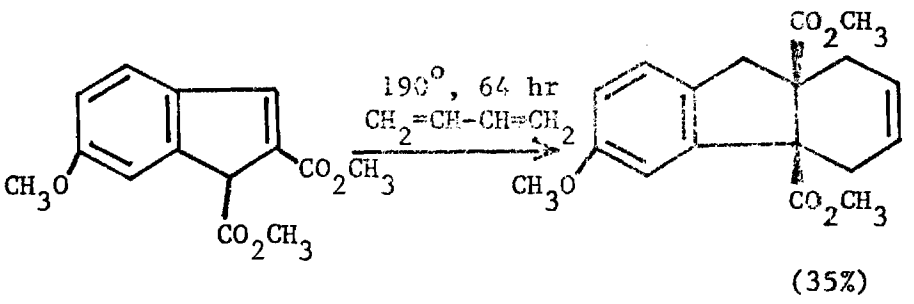


88 89



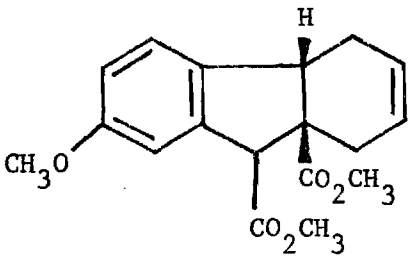
90

SCHEME X (CONTINUED)



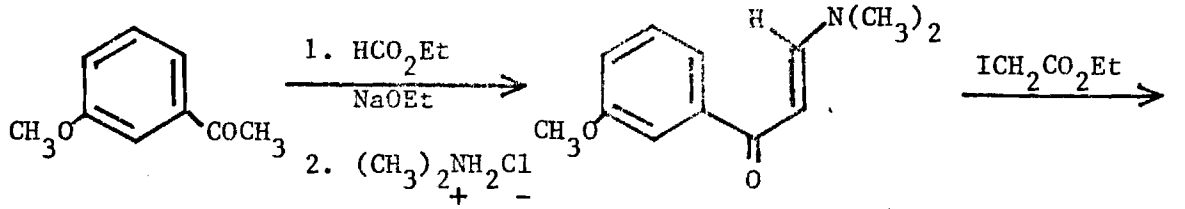
(35%)

91 92

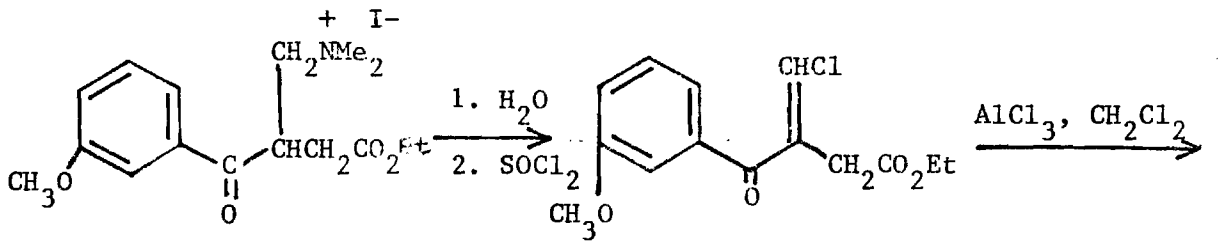


93

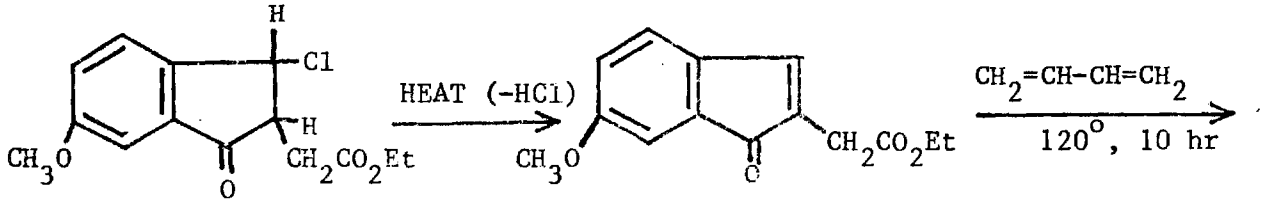
SCHEME XI



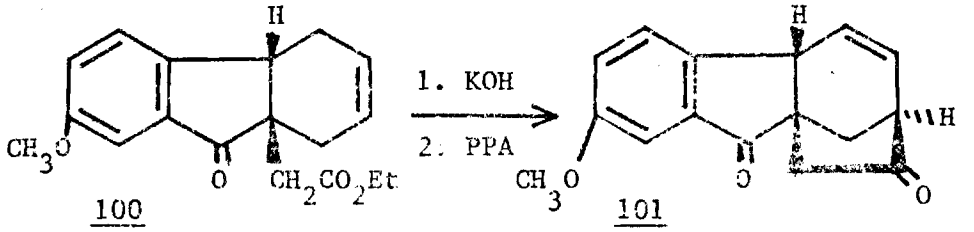
94 95



96 97

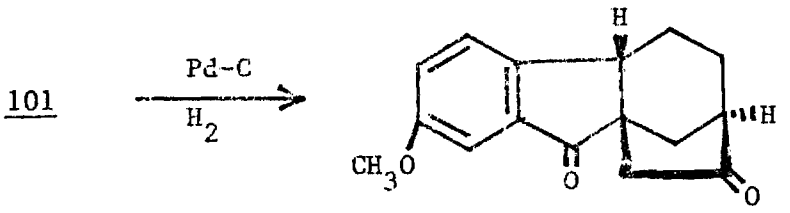


98 99



100 101

SCHEME XI (CONTINUED)



102

References and Notes

1. (a) N. Y. Grigoreva and V. F. Kucherov, Russ. Chem. Rev., 850 (1966); (b) E. Fujita and M. Node, Heterocycles, 1, 709 (1977); (c) For a review of studies of 4 ring preparation see E. J. Zaiko, PhD dissertation in Chemistry, Georgia Institute of Technology, Atlanta, Georgia, 1977.

2. (a) W. Nagata, T. Wakabayashi, Y. Hayose, M. Narisaida, and S. Kamata, J. Am. Chem. Soc., 92, 3202 (1970); (b) W. Nagata, S. Kamata, T. Wakabayashi, M. Narisada, and Y. Hayase, J. Am. Chem. Soc., 93, 5740 (1971); (c) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, J. Am. Chem. Soc., 89, 1483 (1967).

3. K. Mori, M. Shiozaki, N. Itaya, M. Matsui, and Y. Sumiki, Tetrahedron, 25, 1293 (1969).

4. (a) T. Nakata and A. Tahara, Tetrahedron Lett., 18, 1515 (1976); (b) A. Tahara and Y. Ohtsuka, J. Chem. Soc., Perkin 1, 320 (1972); (c) The benzilic acid rearrangement was investigated by J. F. Grove and B. J. Riley, J. Chem. Soc., 1105 (1961).

5. (a) H. J. E. Loewenthal and S. Schatzmuller, J. Chem. Soc., Perkin 1, 2149 (1975); (b) H. J. E. Loewenthal and S. Schatzmuller, Tetrahedron Lett., 31, 3115 (1972).

6. P. N. Chakrabortty, R. Dasgupta, S. K. Dasgupta, S. R. Ghosh, and U. R. Ghatak, Tetrahedron, 29, 4653 (1973).

7. (a) K. Mori, M. Matsui, and Y. Sumiki, Tetrahedron Lett., 6, 429 (1970); (b) K. Mori, Tetrahedron, 27, 4907 (1971).

8. F. Ziegler and M. E. Condon, J. Org. Chem., 36, 3707 (1971).

9. E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, J. Am. Chem. Soc., 92, 396 (1970).

10. (a) A. J. Baker and A. C. Goudie, J. Chem. Soc., Chem. Comm., 180 (1971); (b) Ibid., 951 (1972).

11. (a) H. O. House, C. B. Hudson, and E. J. Racah, J. Org. Chem., 37, 989 (1972); (b) H. O. House and W. C. McDaniel, J. Org. Chem., 42, 2155 (1977).

12. (a) H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, J. Org. Chem., 33, 957 (1968); (b) H. O. House, J. K. Larson, and H. C. Muller, J. Org. Chem., 33, 961 (1968).

13. H. Martens, G. Jammaer, and G. Hoornaert, Tetrahedron, 31, 2293 (1975).

CHAPTER II

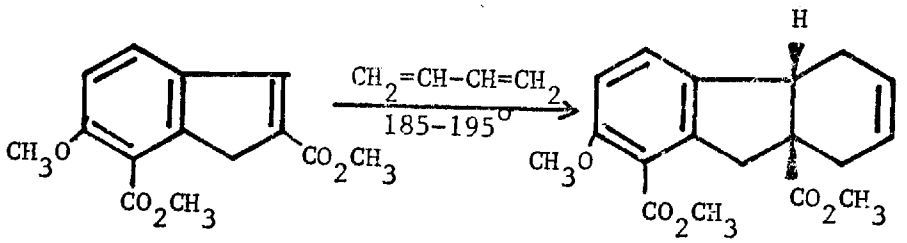
THE USE OF INDENONE KETALS AS DIENOPHILES

Discussion

Previous study[1] of the Diels-Alder reaction of butadiene with the unsaturated ester 1 (Scheme I) established that the rather vigorous conditions required for successful reaction resulted in concurrent double bond isomerization 1⇌2 in the dienophile. Consequently, both the adduct 3, desired as a gibberellin precursor, and the undesired structurally isomeric adduct 4 were produced in comparable amounts. It appeared that this synthetic problem might be solved by use of the indenone 5 as a dienophile since this ketone 5 would not only prevent double bond isomerization but should also be a more reactive dienophile.[2] However, a variety of attempts[3] to convert the readily available indanones 6 to the indenones 5 either by dehydrogenation or by a halogenation-dehydrohalogenation sequence were unsuccessful. Consequently, we were led to study alternative synthetic routes to the indenones 5 or synthetically equivalent structures; the results of this study are reported in this chapter.

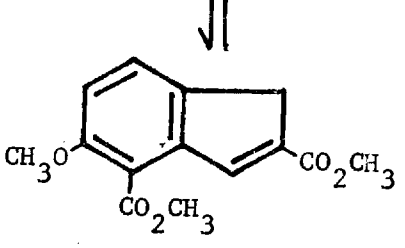
To obtain compounds synthetically equivalent to the indenone esters 5, we chose the indanones 7 (Scheme II) as starting materials, the methoxy ketone 7b being obtained by cyclization of the acid chloride 8b under the special conditions described previously.[4] Previously described procedures[5] were also used to convert the indanone 7b to the keto ester 10. Each monobromo ketone 14 (prepared from the indanone 7, Scheme III) was converted to its ketal 15 which could be further

SCHEME I

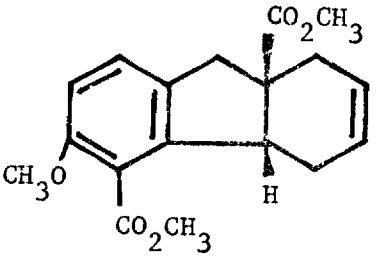


1 ⇌ 2

3 + 4



2



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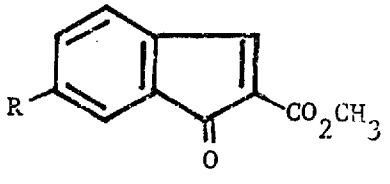
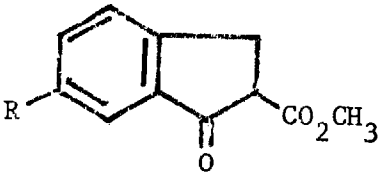


5a, R = H

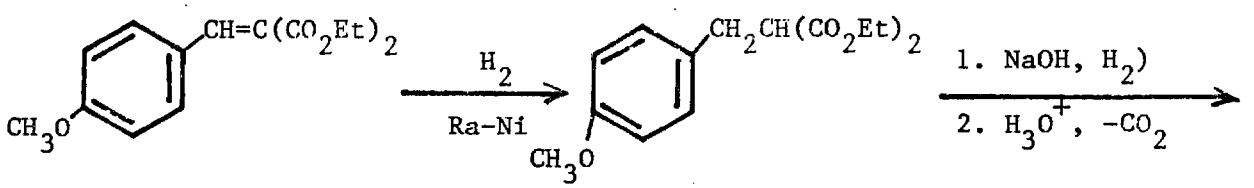
5b, R = CH_3O



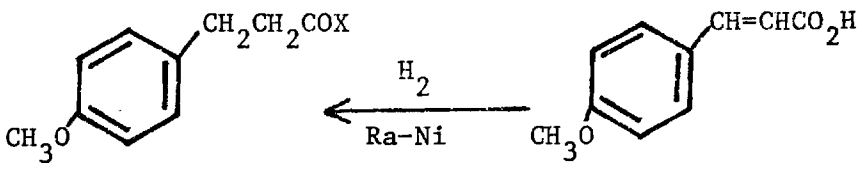
6a, R = H

6b, R = CH_3O

SCHEME II

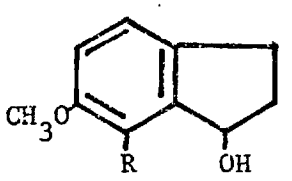


11 12

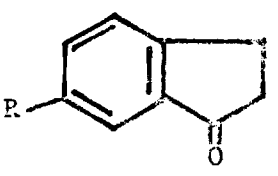


8a, X = OH
b, X = Cl

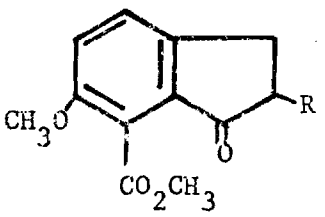
13



9a, R = H
b, R = CO_2H
c, R = CO_2CH_3

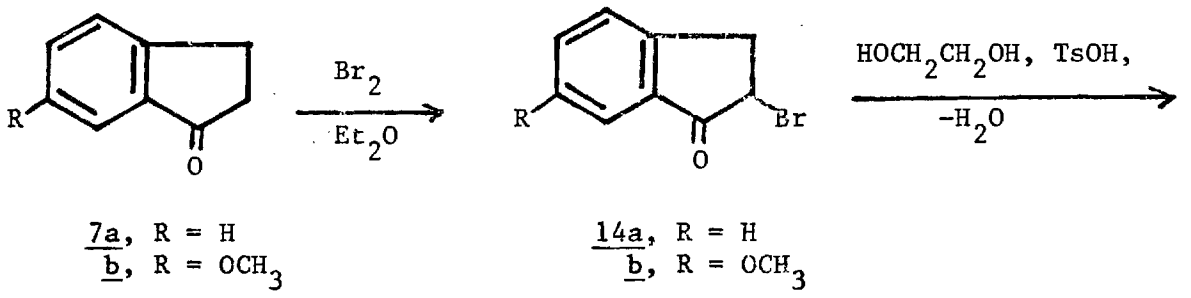


7a, R = H
b, R = OCH_3



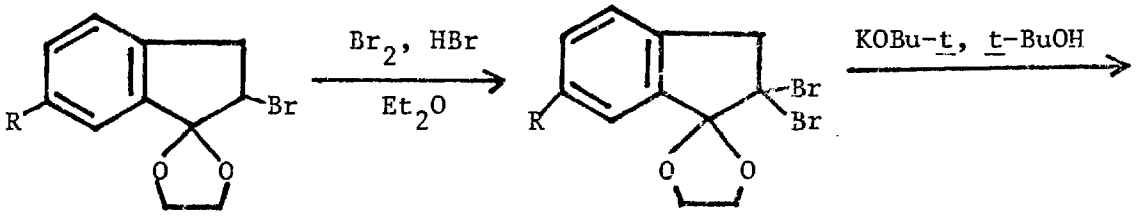
10a, R = H
b, R = CO_2CH_3

SCHEME III



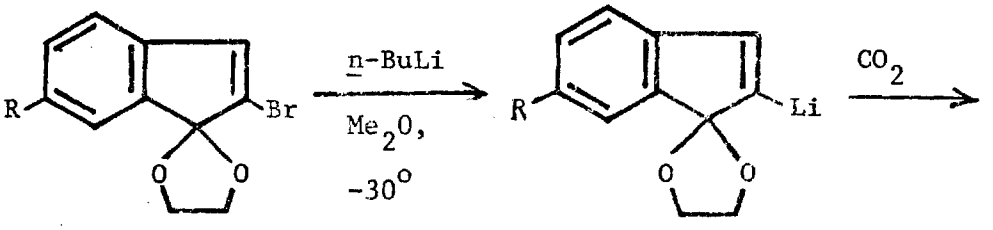
7a, R = H
b, R = OCH_3

14a, R = H
b, R = OCH_3



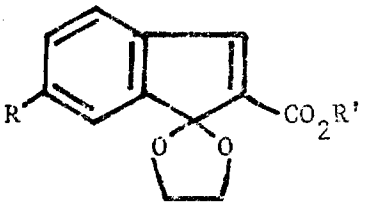
15a, R = H
b, R = OCH_3

17a, R = H
b, R = OCH_3



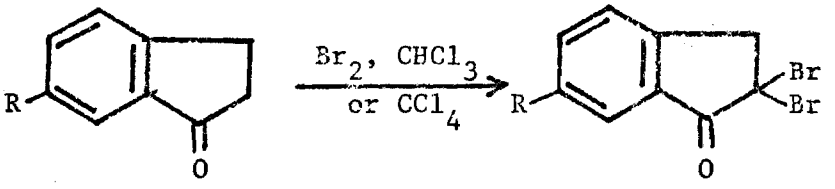
19a, R = H
b, R = OCH_3

20



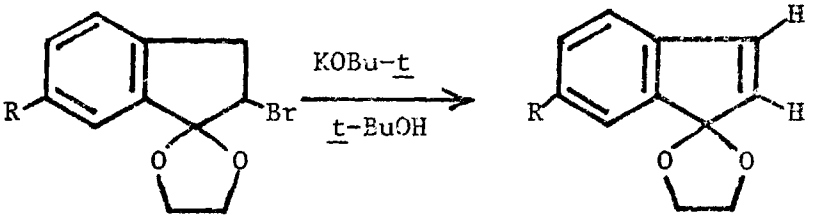
21a, R = R' = H
b, R = H, R' = CH_3
c, R = OCH_3, R' = H
d, R = OCH_3, R' = CH_3

SCHEME III (CONTINUED)



7a, R = H
b, R = OCH_3

16a, R = H
b, R = OCH_3



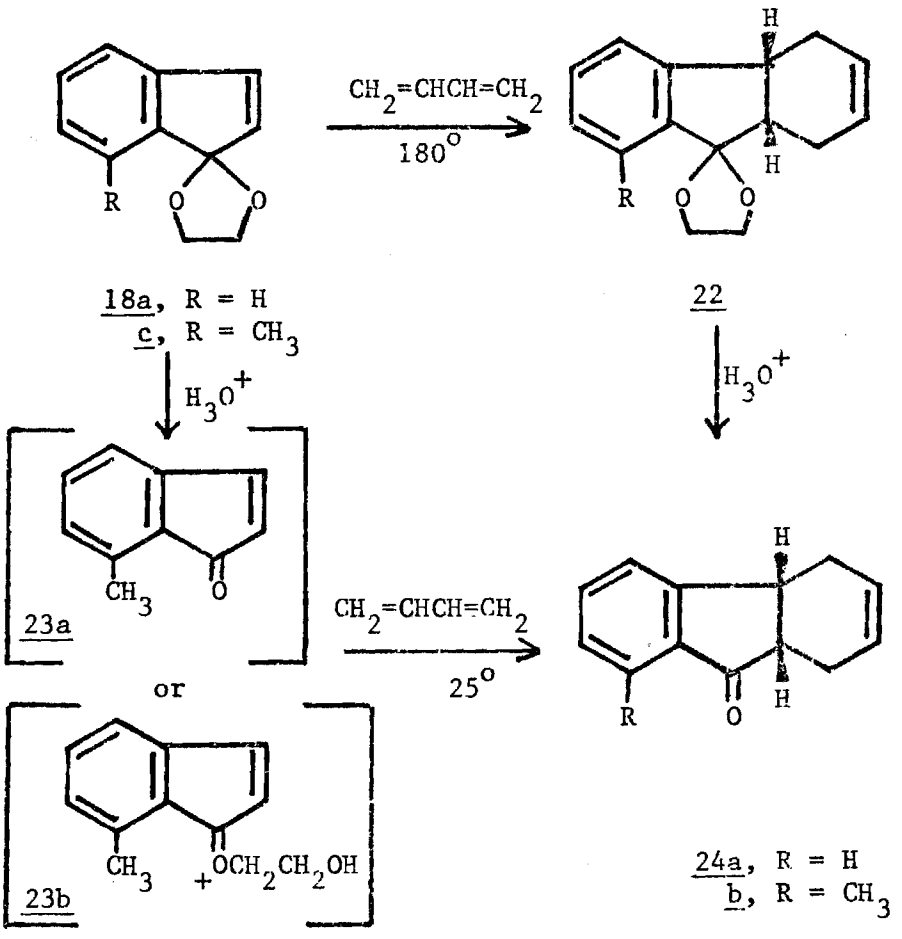
15a, R = H
b, R = OCH_3

18a, R = H
b, R = OCH_3

brominated with Br_2 in Et_2O containing a catalytic amount of HBr[6] to form the dibromo ketal 17. Although the ketal 17a was also successfully prepared from the dibromo ketone 16a, we were unable to form ketal 17b from the dibromo ketone 16b. As had been observed previously with the bromo ketal 15a,[2a] reaction of each of the bromo ketals 15 and 17 with KOBu-t in t-BuOH afforded the indenone ketals 18 and 19 in good yield. Each of the vinyl bromides 19 could be converted to the corresponding organolithium derivative 20 by exchange with n-BuLi. Presumably, the stability of these β-alkoxy organolithium compounds 20 is attributable to the fact that elimination of lithium alkoxide in these cases would produce a highly strained cyclic allene.[7] The only problem we encountered in the formation of the lithium reagents 20 arose because the exchange of n-BuLi with the bromides 19 was very slow in hexane and addition of conventional ethereal co-solvents (Et_2O or THF) resulted in proton abstraction from these ethereal solvents converting an appreciable fraction of the lithium derivatives 20 to the protonated ketals 18. This problem was largely overcome by the use of Me_2O (bp -24°) as an ethereal cosolvent that lacks β-hydrogen atoms and also served to control the temperature of the reaction. Carbonation of the lithio derivatives 20 produced the acids 21a and 21c that were converted to the corresponding esters 21b and 21d for further use.

Earlier study[2a,c] of the Diels-Alder reaction of butadiene with the indenone ketals 18a and 18c (Scheme IV) had indicated that the ketal 18a could be used directly as a dienophile at 180° to form the ketal 22 that was subsequently hydrolyzed to the ketone 24a. Alternatively, treatment of the ketal 18c with aqueous acid generated at least a low

SCHEME IV



18a, R = H
c, R = CH_3

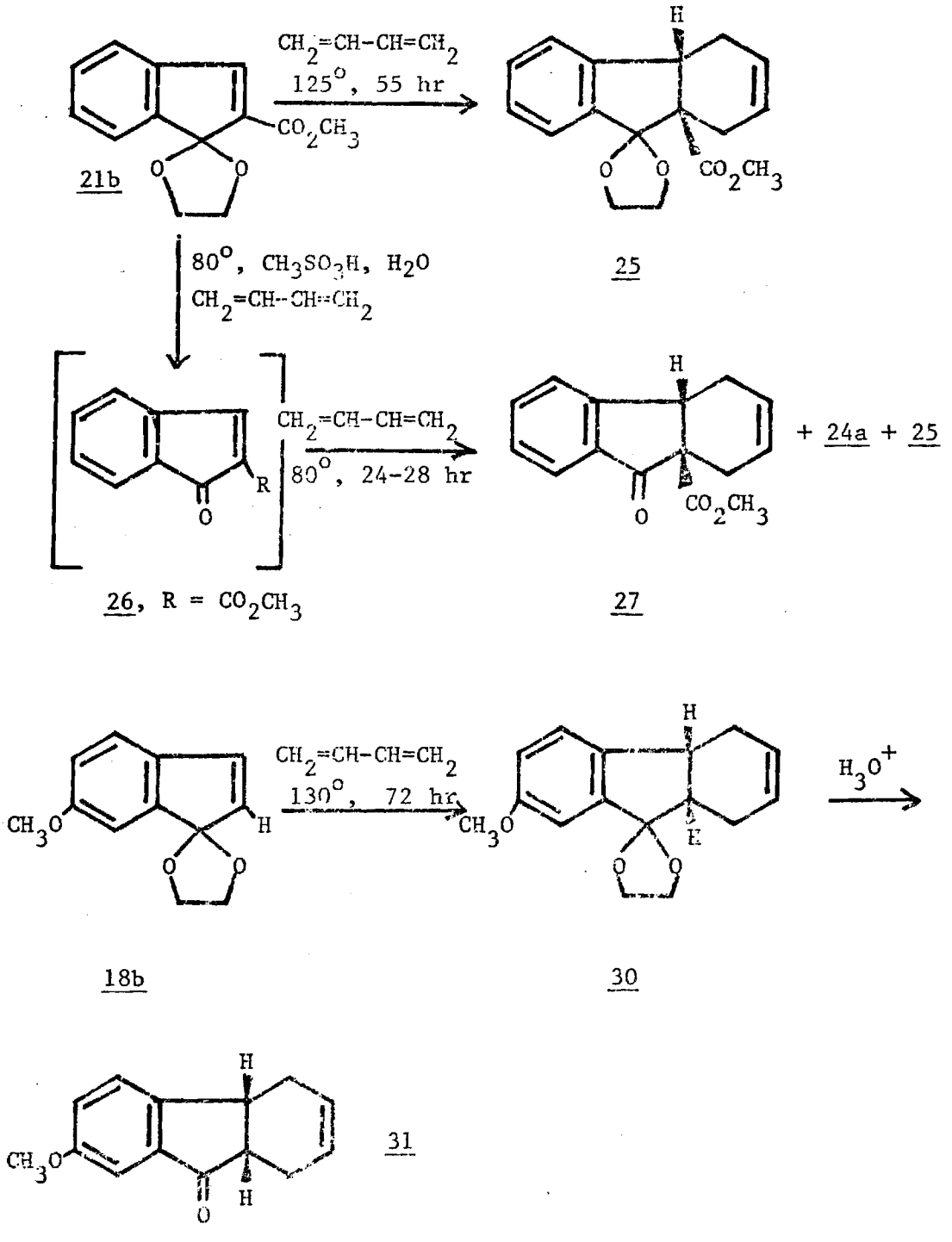
22

23a

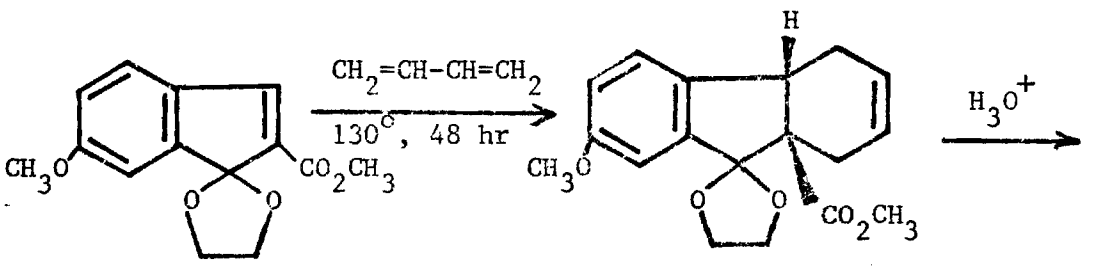
23b

24a, R = H
b, R = CH_3

SCHEME IV (CONTINUED)

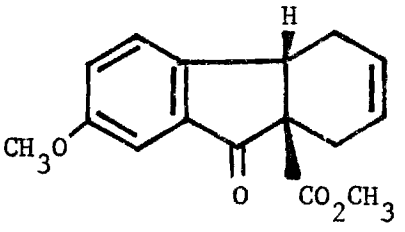


SCHEME IV (CONTINUED)



21d

28



29

concentration of a yellow colored intermediate, thought to be either the indenone 23a or the related oxonium ion 23b, that reacted with butadiene at 25° to form the adduct 24b. To explore these reaction conditions further, the ketal ester 21b was allowed to react either with butadiene alone or with a mixture of butadiene, water, and 0.3 molar equiv of CH_3SO_3H to generate either the indenone 26 or the related oxonium ion (cf. 23b). Although the reaction with butadiene under neutral conditions to form the ketal 25 required somewhat higher temperature and longer reaction time than the acid-catalyzed reaction to form ketone 27, this advantage of the acid-catalyzed process was offset by the formation of the ketone 24a (from hydrolysis and decarboxylation of the ester 27) and a small amount of the ketal 25 as by-products in the acid-catalyzed reaction. Consequently, the reactions of the methoxy indenone ketals 18b and 21d with butadiene were effected under neutral conditions.

We were surprised to find that the reactivities of the two indenone ketals 18b and 21d as dienophiles were similar in spite of the fact that only one ketal, 21d, has an electron-withdrawing carbomethoxyl group conjugated with the reacting double bond. From a series of reactions of these ketals with butadiene at 130° for various periods of time, we estimate that the rate of reaction of butadiene with the ketal 21d is approximately twice the rate of the corresponding reaction with the ketal 18b. Thus, the major factor responsible for the reactivity of these materials as dienophiles appears to be the presence of a strained C=C in the indene systems (cf. cyclopentadiene). It is likely that the 180° reaction temperature used in the earlier study[2a] with the indenone ketal 18a was well above the minimum temperature required for reaction.

In any case, the use of the indenone ketal 21d as the dienophile in a reaction with butadiene provides a synthetically useful route to the tricyclic gibberellin intermediated 28 and 29 and avoids the problem of C=C isomerization encountered in our previous study of the Diels-Alder reaction with the indene 1.

Experimental Section[8]

Preparation of 6-Methoxy-1-indanone (7b)

Condensation of anisaldehyde with diethyl malonate by a standard procedure[9] yielded 94% of the arylidene malonate 11 as a colorless liquid, bp 181-185° (0.85 mm), n^{25}_{D} 1.5578 (lit.[10] bp 130-147° (0.13 mm)). An EtOH solution of this diester 11 was hydrogenated over Ra-Ni[11] at 4 atm and 25° to yield 96.5% of the diester 12, bp 186-190.5° (1.3 mm), n^{25}_{D} 1.4964 (lit.[10] bp 138-142° (0.2 mm), n^{27}_{D} 1.4928). After saponification of the diester 12 and subsequent decarboxylation, reaction of the resulting crude acid 8a with excess refluxing $SOCl_2$ yielded 76.5% of the acid chloride 8b as a pale yellow liquid, bp 170-174° (15 mm), n^{25}_{D} 1.5323-1.5331 (lit.[10] bp 95-97° (0.2 mm)). When intermediates were not isolated, the diester 11 could be converted to the acid chloride 8b, bp 159-163° (10 mm), in an overall yield of 78.4%.

Alternatively, condensation of anisaldehyde with malonic acid yielded 83.2% of the cinnamic acid 13, mp 171.4-173.3° (lit.[12] mp 173°). Hydrogenation of a slurry of this acid 13 in EtOH over Ra-Ni at 4 atm and 25° yielded 94.8% of the crude acid 8a, mp 95-102° (lit.[13] mp 103.5-104°). Reaction of this crude acid 8a with excess refluxing $SOCl_2$ yielded 88.8% of the acid chloride 8b, bp 120-122.8° (2.4-3.3 mm), n^{25}_{D} 1.5360. The same acid chloride 8b was obtained in 87% yield by

reaction of the crude acid 8a with excess refluxing $(COCl)_2$. A previously described cyclization procedure[4] employing a dilute solution of the acid chloride 8b and $AlCl_3$ in CH_2Cl_2 yielded 77.5% of the indanone 7b, mp 104.3-107.3° (lit.[4] mp 109-110°).

Preparation of the Keto Ester 10b

After reduction of the ketone 7b with $LiAlH_4$ in Et_2O to form 94.4% of the crude alcohol 19a, mp 43.7-44.9° (lit.[5] mp 46-47.5°), use of the previously described[5] reaction of the alcohol 9a with n-BuLi in hexane followed by carbonation on dry ice yielded 61.5% of the hydroxy acid 9b, mp 154.5-156.7° dec (lit.[5] mp 150-151° to 160-161° with decomposition), accompanied by 16% recovery of starting alcohol 9a. Esterification with excess ethereal CH_2N_2 followed by recrystallization from pentane yielded 77% of the hydroxy ester 9c, mp 53-56° (lit.[5] mp 55-55.5°). Oxidation of this alcohol yielded 85% of the keto ester 10a, mp 123-125° (lit[6] mp 127-127.5°). Reaction[5] of 10a with sodium hydride and dimethyl carbonate in benzene followed by recrystallization from methanol yielded 35% of the keto diester 10b, mp 118.5-124.8° (lit.[5] mp 120-125°) that was identified with a previously described[5] sample by comparison of ir, nmr, and mass spectra.

Preparation of 1-Indanone (7a)

Cyclization of hydrocinnamic acid with polyphosphoric acid at 70-85° yielded 83% of the ketone 7a, bp 119-125° (10-15 mm), that solidified on standing, mp 36-38.7° (lit.[2a] mp 40-41°). When the same cyclization was effected with a mixture of P_2O_5 and CH_3SO_3H,[14] a 64% yield of ketone 7a was obtained. Reaction of propiolactone and $AlCl_3$ with excess refluxing benzene[15] yielded 60% of the same ketone 7a.

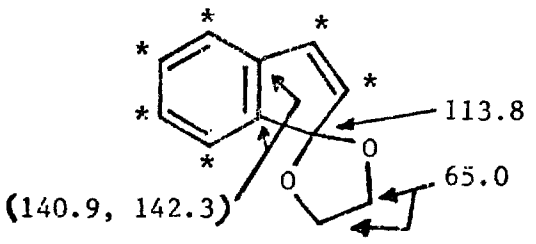
Preparation of the Dibromoindanone 16a and the Ketal 17a

Reaction of the indanone 7a with 1 molar equiv of Br_2 in Et_2O at 3° yielded, after filtration through decolorizing carbon and removal of the solvent under vacuum, 86% of the crude bromo ketone 14a as a cream colored solid (lit.[2a] mp37-38.5°). A solution of 16.2 g (76.7 mmol) of this crude bromo ketone 14a, 4.76 g (76.7 mmol) of $HOCH_2CH_2OH$, and 0.15 g of p-TsOH in 125 ml of PhH was refluxed for 78 hr with continuous separation of H_2O. During the reflux period two additional 1.54 g (24.8 mmol) portions of $HOCH_2CH_2OH$ were added. The resulting solution was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, and distilled to separate 15.39 g (78.6%) of the crude ketal 15a as a pale yellow liquid, bp 93-97.5° (0.02-0.03 mm), $n^{25}D$ 1.5765-1.5779 (lit.[2a] bp 95-105° (3.5 mm)); ir (CCl_4), weak absorption at 1745 and 1730 cm^{-1} (C=O of bromo ketone impurity), nmr (CCl_4), δ 6.9-7.5 (4H, m, aryl CH), 3.9-4.7 (5H, m, CH_2O and CHBr), and 2.8-3.7 (2H, m, benzylic CH_2); mass spectrum, m/e (rel. intensity), 256 (M^+, 2), 254 (M^+, 2), 175 (100), 146 (44), 131 (60), 103 (47), 77 (28), and 51 (20).

After 7.6 g (29.8 mmol) of the bromo ketal 15a had been stirred at 25° for 6 hr with a solution of 43.5 mmol of KOBu-t in 50 ml t-BuOH, the dark colored reaction mixture was partitioned between H_2O and Et_2O. The ethereal layer was washed with aqueous NaCl, dried, concentrated, and distilled to separate 3.27 g (63%) of the unsaturated ketal 18a as a colorless liquid, bp 85-87° (0.1 mm), $n^{25}D$ 1.5717-1.5723 (lit.[2a] bp 78-80° (0.15 mm), $n^{28}D$ 1.5699); ir (CCl_4), 1615 cm^{-1} (C=C); mass spectrum, m/e (rel. intensity), 174 (M^+, 31), 118 (100), 115 (18), 102 (21), and 90 (24). The ^{13}C nmr spectrum of this ketal 18a ($CDCl_3$

solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements.

(* 121.0, 121.6, 126.1, 129.1, 132.4, 134.0 ppm)



After HBr gas had been passed through a cold (0°) solution of 39.09 g (153 mmol) of the bromo ketal 15a in 600 ml of Et_2O, 24.5 g (153 mmol) of Br_2 was added, dropwise and with stirring during 15 min.[6] After the resulting mixture had been stirred for 2 hr at 25°, it was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried (Na_2SO_4) and concentrated to leave 52.8 g of crude product as a pale yellow solid. Recrystallization of this material from CCl_4 separated 32.56 g (63.6%) of the dibromo ketal 17a as fine, pale yellow crystals, mp 88-89.9°, as well as a 6.2 g fraction of less pure material, mp 67-84°, that contained (ir analysis) ketone impurities.

In an alternative preparation, a $CHCl_3$ solution of the indanone 7a was treated with 2 molar equiv of Br_2 to yield the dibromo ketone 16a as yellow prisms from EtOH, mp 131-133.8° (lit.[2a] mp 133-134°); ir (CCl_4), 1745 cm^{-1} (C=O); nmr (CCl_4), δ 7.2-8.1 (4H, m, aryl CH), and 4.27 (2H, s, benzylic CH_2). A solution of 8.12 g (28 mmol) of the dibromo ketone 16a. 1.74 g (28 mmol) of the $HOCH_2CH_2OH$, and 0.15 g p-TsOH in 50 ml of PhH was refluxed for 96 hr with continuous separation of H_2O. During this reflux period two additional 0.58 g (9.3 mmol) portions of

$HOCH_2CH_2OH$ were added. After the PhH solution had been washed successively with aqueous $NaHCO_3$, H_2O, and aqueous NaCl, it was concentrated to separate various crops of crystalline solid melting within the range 68-83° and containing (ir analysis) mixtures of the ketone 16a and the ketal 17a. Repeated recrystallization from CCl_4 and final sublimation (80° and 0.05 mm) separated a small sample of the pure ketal 17a as a white solid, mp 86-87.8°; ir (CCl_4), no C=O absorption; nmr (CCl_4), δ 7.0-7.6 (4H, m, aryl CH), 4.1-4.7 (4H, m, CH_2O), and 3.85 (2H, s, benzylic CH_2); uv max (95% EtOH), 258 nm (ε 750), 265 nm (ε 990), and 272.5 nm (ε 1050); mass spectrum, m/e (rel. intensity), 336 (M^+, 40), 334 (M^+, 81), 332 (M^+, 43), 255 (100), 253 (98), 211 (32), 209 (35), 148 (90), 118 (43), 115 (30), 104 (32), 102 (64), 101 (32), and 75 (32).

Anal. Calcd for $C_{11}H_{10}Br_2O_2$: C, 39.56; H, 3.02; Br, 47.84. Found: C, 39.66; H, 3.04; Br, 47.83.

Preparation of the Unsaturated Ketal 19a

A solution of 32.36 g (96.9 mmol) of the ketal 17a and KOBu-t (from 5.3 g or 136 mg-atm of K) in 127 ml of t-BuOH was stirred at 25-27° for 36 hr and then partitioned between Et_2O and cold H_2O. The Et_2O solution was washed with aqueous NaCl, dried (Na_2SO_4), and concentrated to leave 23.67 g (96.5%) of the ketal 19a as a cream-colored solid, mp 71.2-74°. Recrystallization from hexane afforded the pure ketal 19a as colorless needles, mp 72.7-73.5°: ir (CCl_4), 1617 cm^{-1} (conjugated C=C); nmr (CCl_4), δ 6.8-7.4 (4H, m, aryl CH), 6.61 (1H, s, vinyl CH), and 3.9-4.6 (4H, m, CH_2O); uv max (95% EtOH), 217 nm (ε 35,700), 222 nm (ε 32,200), 283 nm (ε 4200), 294 nm (ε 4100), and 311 nm (ε 2900);

mass spectrum, m/e (rel. intensity), 254 (M^+, 17), 252 (M^+, 17), 173 (100), 129 (32), 115 (22), 101 (29), and 89 (24).

Anal. Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58. Found: C, 52.21; H, 3.62; Br, 31.50.

Preparation of the Unsaturated Ester 21b

To a cold (-24°) solution of 3.68 g (14.5 mmol) of the bromide 19a in 100 ml of Me_2O was added, dropwise and with stirring, 9.2 ml of a hexane solution containing 14.6 mmol of n-BuLi. After the resulting deep blue solution had been stirred at -25° for 10 min, it was siphoned onto crushed dry ice with accompanying change in the color of the solution from blue to red to orange. The resulting mixture was partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. Concentration of the organic solution left 0.56 g of brown liquid with nmr absorption corresponding to the known[2a] ketal 18a accompanied by a small amount of the starting bromo ketal 19a. After the aqueous solution had been acidified to pH 2 with cold (5°) aqueous 6 M HCl, it was extracted with CH_2Cl_2 and the organic extract was washed with aqueous NaCl, dried (Na_2SO_4), and concentrated. The residual crude acid 21a (2.46 g of tan solid) was recrystallized from CH_2Cl_2-hexane to separate 1.98 g (62.4%) of fractions of the acid 21a as white solids melting within the range 185-189° dec; ir ($CHCl_3$), 2970 (broad, carboxyl OH), 1685 (carboxyl C=O), and 1612 cm^{-1} (conjugated C=C); uv max (95% EtOH), 224 nm (ε 24,900), 228 nm (ε 24,000), and 313 nm (ε 7500); nmr ($CDCl_3$), δ 11.16 (1H, s, OH), 7.68 (1H, s, vinyl CH), 7.1-7.4 (4H, m, aryl CH), and 4.1-4.8 (4H, m, CH_2O). Attempts to effect this same metallation, 19a → 20, with n-BuLi in hexane at 0° resulted in recovery of about half of the unchanged

bromide 19a and use of Et_2O at -35° as a reaction solvent resulted in the formation of increased amounts of the crude olefin 18a. A cold (-30°) solution of 2.2 g (0.79 mmol) of the bromide 19a in 25 ml of THF was treated with 0.5 ml of a hexane solution containing 0.79 mmol of n-BuLi, stirred at -30 to -35° for 30 min, and then quenched by the dropwise addition of 0.25 ml of D_2O. The recovered crude product (a mixture of the olefin 18a and a small amount of starting bromide, nmr analysis) was subjected to preparative tlc separation on silica gel to separate a sample of the pure olefin 18a with nmr doublets (J=5.6 Hz) of equal intensity at δ 6.46 and 5.98 corresponding to the vinyl CH groups of the non-deuterated olefin 18a.

The acid 21a (5.30 g or 24.3 mmol) was added to 235 ml of Et_2O containing 25.1 mmol of CH_2N_2. The resulting mixture was stirred at 25° for 5 min and then concentrated and partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal layer was dried and concentrated to leave 5.58 g (99%) of the ester 21b (nmr analysis) as a pale yellow liquid that solidified on standing, mp 42.8-49°. Recrystallization from pentane separated the pure ester 21b as a waxy white solid, mp 47.8-50°; ir (CCl_4), 1722 (conjugated ester C=O) and 1615 cm^{-1} (conjugated C=C); uv max (95% EtOH), 224 nm (ε 21,900), 231 nm (ε 21,600), and 315 nm (ε 6900); nmr (CCl_4), δ 7.33 (1H, s, vinyl CH), 7.0-7.3 (4H, m, aryl CH), 3.9-4.6 (4H, m, CH_2O), and 3.67 (3H, s, OCH_3); mass spectrum, m/e (rel. intensity), 232 (M^+, 4), 189 (8), 173 (12), 157 (52), 101 (21), 85 (79), 83 (100), 48 (20), and 47 (31).

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.95; H, 5.13.

In another experiment employing 12.66 g (50 mmol) of the bromide 19a, the crude acid 21a obtained (7.97 g, mp 183-187° dec) was directly esterifed with ethereal CH_2N_2 to yield 7.96 g (69% overall yield) of the ester 21b, mp 44-49°.

Preparation of the Bromo Ketone 14b

To a cold (0-5°) solution of 4.05 g (25 mmol) of the ketone 7b in 400 ml of Et_2O was added, dropwise and with stirring during 8 min, 4.00 g (25 mmol) of Br_2. The resulting colorless solution was washed successively with aqueous $NaHCO_3$ and aqueous NaCl, and then dried and concentrated to leave 6.18 g of residual yellow liquid that solidified on standing. Recrystallization from hexane separarated 3.17 g (53%) of the crude bromo ketone 14b as various fractions of colorless to cream-colored plates melting within the range 45-60°. This material turned pink upon exposure to the air and light. Chromatography of a portion of this material on silica gel with an Et_2O-hexane eluent (1:9 v/v) followed by crystallization from hexane separated a sample of the pure bromo ketone 14b as white plates, mp 60-62°; ir (CCl_4), 1720 cm^{-1} (C=O); uv max (95% EtOH), 220 nm (ϵ 21,200), 256 nm (ϵ 8800), and 332 (ϵ 3300); nmr (CCl_4), δ 6.9-7.4 (3H, m, aryl CH), 4.4-4.7 (1H, m, CHBr), and 3.0-4.0 (5H, m, aliphatic CH including a CH_3O singlet at 3.78); mass spectrum, m/e (rel. intensity), 242 (M^+, 40), 240 (M^+, 44), 162 (22), 161 (100), 133 (26), 89 (22), and 63 (20).

Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76; Br, 33.14. Found: C, 49.80; H, 3.77; Br, 33.23.

Preparation of the Dibromo Ketone 16b

To a solution of 4.05 g (25 mmol) of the ketone 7b in 400 ml of

CCl_4 was added, dropwise and with stirring, 8.0 g (50 mmol) of Br_2. The resulting red solution was washed successively with H_2O, aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and aqueous NaCl and then dried and concentrated. Recrystallization of the residual orange solid from hexane separated 5.67 g (71%) of the crude ketone 16b as orange plates melting within the range 103.6-107°. Recrystallization from hexane afforded the pure ketone 16b as white prisms, mp 107.1-107.9°; ir (CCl_4), 1738 cm^{-1} (C=O); uv max (95% EtOH), 219 nm (ε 20,800), 263 nm (ε 9400), and 344 nm (ε 3300); nmr (CCl_4), δ 7.2-7.4 (3H, m, aryl CH), 4.18 (2H, s, benzylic CH_2), and 3.91 (3H, s, OCH_3); mass spectrum, m/e (rel. intensity), 322 (M^+, 43), 320 (M^+, 86), 318 (M^+, 44), 242 (21), 241 (76), 240 (30), 239 (71), 161 (38), 160 (100), 132 (24), 89 (25), and 63 (20).

Anal. Calcd for $C_{10}H_8Br_2O_2$: C, 37.53; H, 2.52; Br, 49.95. Found: C, 37.56; H, 2.52; Br, 49.92.

Preparation of the Ketal 15b

A solution of 14.86 g (61.6 mmol) of the ketone 14b, 3.82 g (61.5 mmol) of $HOCH_2CH_2OH$, and 20 mg p-TsCH in 100 ml of PhH was refluxed for 3 days with continuous separation of H_2O; additional 2.0 g (32.2 mmol) quantities of $HOCH_2CH_2OH$ were added after 24 and 48 hr. The resulting mixture was partitioned between PhH and aqueous $NaHCO_3$ and the organic layer was washed with H_2O and with aqueous NaCl and then dried and concentrated. The crude solid product (16.47 g) was recrystallized from hexane to separate 3.67 g (21%) of fractions of the ketal 15b as tan prisms melting in the range 81.7-85° as well as 2.25 g of less pure product, mp 70.3-73.2°. A portion of this material was sublimed under reduced pressure to separate the pure ketal 15b as a colorless solid

mp 83.2-83.7°; ir (CCl_4), 1282 and 1215 cm^{-1} (ketal C-O) with no absorption attributable to a C=O function; uv max (95% EtOH), 216 nm (shoulder, ϵ 9700), 285 nm (ϵ 3000), and 292 nm (ϵ 2700); nmr ($CDCl_3$), δ 6.7-7.3 (3H, m, aryl CH), 4.53 (1H, t, J = 7 Hz, CHBr), 4.1-4.4 (4H, m, CH_2O), 3.78 (3H, s, OCH_3), and 3.0-3.4 (2H, m, benzylic CH_2); mass spectrum, m/e (rel. intensity), 286 (M^+, 6), 284 (M^+, 6), 206 (14). 205 (100), and 161 (25).

Anal. Calcd for $C_{12}H_{13}BrO_3$: C, 50.55; H, 4.60; Br, 28.02. Found: C, 50.58; H, 4.62; Br, 28.10.

Preparation of the Ketal 17b[6]

Bromine was added, dropwise and with stirring, to a solution (at 26°) of 1.37 g (4.8 mmol) of the ketal 15b in 25 ml of Et_2O containing a catalytic amount of anhydrous HBr, until a red color persisted in the solution. The resulting red solution was stirred for 5 min with an aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ and then the colorless ethereal phase was washed with aqueous $NaHCO_3$ and aqueous NaCl, dried, and concentrated. The residual solid ketal 17b (1.50 g or 86%, mp 131-136°) was recrystallized from hexane to separate 1.33 g (76%) of fractions melting within the range 130.1-138.8°. An additional recrystallization afforded the pure ketal 17b as colorless prisms, mp 137.4-139.1°;ir (CCl_4), 1285 and 1220 (ketal C-O); uv max (95% EtOH), 217 nm (shoulder, ϵ 10,700), 285 nm (ϵ 3000), and 292 nm (ϵ 2800); nmr ($CDCl_3$), δ 6.7-7.3 (3H, m, aryl CH), 4.2-4.7 (4H, m, CH_2O), 3.87 (2H, s, benzylic CH_2), and 3.80 (3H, s, OCH_3); mass spectrum, m/e (rel. intensity), 366 (M^+, 25), 364 (M^+, 48), 362 (M^+, 27), 285 (96), 283 (100), 178 (41), 160 (70), 148 (53), 120 (36), 89 (48), 63 (45), and 51 (32).

Anal. Calcd for $C_{12}H_{12}Br_2O_3$: C, 39.59; H, 3.32; Br, 43.90. Found: C, 39.54; H, 3.33; Br, 44.06.

An attempt to prepare the dibromo ketal 17b by reaction of the dibromo ketone 16b with $HOCH_2CH_2OH$ resulted in recovery of 97% of the starting ketone 16b.

Preparation of the Unsaturated Ketal 19b

A slurry of 22.52 g (62 mmol) of the ketal 17b in 100 g of t-BuOH was treated, portionwise and with stirring during 3 min, with t-BuOK, from 3.93 g (0.10 g-atom) of K and 78.6 g of t-BuOH. After the mixture had been stirred at 25-30° for 4 hrs, it was partitioned between H_2O and Et_2O. After the ethereal solution had been washed with aqueous NaCl and dried, concentration left 17.28 (98.7%) of the crude ketal 19b as a cream-colored solid, mp 91-93.7°. Recrystallization gave the pure ketal 19b as a colorless powder, mp 93-93.9°; ir (CCl_4), 1605 (C=C), 1288, and 1211 cm^{-1} (ketal C-O); uv max (95% EtOH), 227 nm (ε 49,000), 287 nm (ε 930), 297 nm (ε 800), and 328 nm (ε 300); nmr ($CDCl_3$), δ 6.5-7.1 (4H, m, vinyl and aryl CH), 4.1-4.5 (4H, m, CH_2O), and 3.74 (3H, s, OCH_3); mass spectrum, m/e (rel. intensity), 284 (M^+, 32), 282 (M^+, 32), 203 (100), 175 (21), 147 (48), 119 (26), and 116 (20).

Anal. Calcd for $C_{12}H_{11}BrO_3$: C, 50.91; H, 3.92; Br, 28.22. Found: C, 50.82; H, 3.96; Br, 28.31.

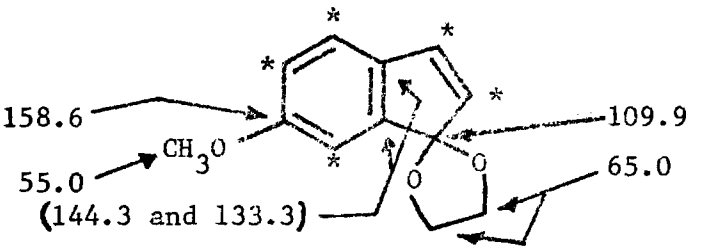
In a larger scale preparation, 40.54 g (0.25 mol) of the ketone 7b was brominated in Et_2O and crude bromo ketone 14b (56.98 g of yellow solid) was converted to the ketal 15b. The crude ketal 15b was brominated and the crude dibromo ketal 17b (91.5 g, contains ca. 5% of the dibromo ketone 16b) was treated with 0.358 mol of KOBu-t in t-BuOH. Application

of the previously described isolation procedure afforded 56.8 g of the crude ketal 19b as a tan solid. Recrystallization from hexane separated 44.75 g (63% based on the ketone 7b) of the pure ketal 19b, mp 90.7-93.8°, accompanied by 11.19 g (15%) of fractions containing less pure ketal 19b (melting within the range 80-91°) that were also suitable for conversion to the ester 21d.

Preparation of the Unsaturated Ketal 18b

A mixture of 5.70 g (20 mmol) of the bromo ketal 15b, 28 mmol of KOBu-t, and 30 ml of t-BuOH was stirred at 25° for 18 hr and then partitioned between H_2O and Et_2O. The ethereal layer was washed with aqueous NaCl, dried over Na_2SO_4, concentrated, and distilled to separate 3.64 g (89%) of the ketal 18b as a colorless liquid, bp 110-115° (0.2 mm), $n^{25}D$ 1.5751-1.5753; ir (CCl_4), 1609 cm^{-1} (C=C); uv max (95% EtOH), 221 nm (ε 21,700), 280 nm (ε 7200), 287 nm (shoulder, ε 6300), and 317 nm (ε 1700); ^1H nmr (CCl_4), δ 6.5-7.0 (3H, m, aryl CH), 6.47 (1H, d, J = 6 Hz, vinyl CH), 5.93 (1H, d, J = 6 Hz, vinyl CH), 3.8-4.2 (4H, m, CH_2O), and 3.64 (3H, s, OCH_3); mass spectrum, m/e (rel. intensity), 204 (M^+, 27), 148 (46), 120 (40), 58 (95), 43 (100), and 42 (22). The ^{13}C nmr spectrum of the product ($CDCl_3$ solution) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.

(*132.3, 132.1, 121.4, 113.6, and 112.6 ppm)



Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.66; H, 5.94.

The ketal 18b was also obtained by reaction of 2.83 g (10 mmol) of the bromo ketal 19b in 80 ml of Me_2O (at -30°) with 6.8 ml of a hexane solution containing 11 mmol of n-BuLi. After the solution had been stirred at -30° for 10 min, it was poured into a mixture of 100 ml of Et_2O and 30 ml of MeOH. After the reaction mixture had been partitioned between H_2O and Et_2O, the ethereal layer was dried, concentrated, and distilled to separate 1.65 g (81%) of the ketal 18b, bp 115-120° (0.1 mm), $n^{25}D$ 1.5768, that was identified with the previously described sample by comparison of nmr and ir spectra.

Preparation of the Ketal Acid 21c

To a solution of 14.16 g (50 mmol) of the bromide 19b in 400 ml of cold (-30°) Me_2O (bp -24°) was added, dropwise and with stirring during 5 min, 31.0 ml of a hexane solution containing 50.2 mmol of n-BuLi. After the resulting cold solution had been stirred for 10 min, it was poured onto dry ice. The resulting mixture was partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O layer was washed with aqueous NaCl, dried, and concentrated to leave a pale yellow liquid with nmr absorption indicating it to be the crude ketal 18b. The aqueous

$NaHCO_3$ solution was cautiously acidified with cold aqueous HCl and extracted with Et_2O. The ethereal extract was washed with aqueous NaCl, dried, and concentrated, to leave 8.77 g (71%) of the acid 21c as a white solid, mp 191-193° dec. Recrystallization from a $CHCl_3$-hexane mixture separated the acid 21c, mp 195-198° dec. A subsequent recrystallization sharpened the decomposition point of the aicd 21c to mp 197-198° dec; ir ($CHCl_3$), 2950 (broad, associated OH), 1680 (carboxyl C=O), and 1608 cm^{-1} (C=C); uv max (95% EtOH), 237 nm (ε 17,000), 306 nm (ε 7200), 315 nm (ε 8400), and 341 nm (ε 10,000); nmr (CD_3COCD_3), δ 7.57 (1H, s, vinyl CH), 6.7-7.4 (3H, m, aryl CH), 4.1-4.6 (4H, m, CH_2O), and 3.84 (3H, s, OCH_3); mass spectrum, m/e (rel. intensity), 248 (M^+, 61), 203 (34), 188 (24), 187 (100), 164 (38), 147 (23), 63 (20), and 44 (40).

Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.61; H, 4.81.

Preparation of the Unsaturated Ester 21d

The ketal acid 21c (2.48 g or 10.0 mmol) was added, portionwise and with stirring during 10 min, to 300 ml of an Et_2O solution containing 11.7 mmol of CH_2N_2. The resulting solution was concentrated and the residual orange solid (2.708 g) was recrystallized from hexane to separate 1.998 g (76%) of the crude ester 21d, mp 110-114°. Recrystallization afforded the pure ester 21d as yellow prisms, mp 114.8-115.3°; ir (CCl_4), 1718 (conj. ester C=O) and 1610 cm^{-1} (conj. C=C); uv max (95% EtOH), 240 nm (ε 15,600), 303 nm (shoulder, ε 6100), 314 nm (ε 7800), and 343 nm (ε 10,400); nmr ($CDCl_3$), δ 7.46 (1H, d, J=0.9 Hz, vinyl CH), 6.6-7.3 (3H, m, aryl CH), 4.0-4.7 (4H, m, CH_2O), 3.77 (3H, s, OCH_3), and 3.75 (3H, s, OCH_3); mass spectrum, m/e (rel. intensity), 262 (M^+, 42), 203 (24), 187 (100), and 163 (24).

Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.20; H, 5.42.

Reaction of the Ketal Ester 21b with Butadiene under Neutral Conditions

A solution of 470 mg (2.02 mmol) of the ester 21b in 1.71 g (31.6 mmol) of butadiene was heated to 125° for 55 hr in a sealed tube and then cooled and concentrated. Distillation of the residual yellow viscous liquid in a short-path still at 0.12 mm pressure separated 450 mg (78%) of the adduct 25 as a colorless, viscous liquid, $n^{25}D$ 1.5531; ir (CCl_4) 1735 (ester C=O) and 1662 cm^{-1} (weak, C=C); uv max (95% EtOH), a series of weak maxima (ε 335-748) in the region 237-272 nm with an additional maximum at 306 nm (ε 399); nmr ($CDCl_3$), δ 7.0-7.4 (4H, m, aryl CH), 5.3-6.0 (2H, m, vinyl CH), 3.8-4.4 (5H, m, CH_2O and benzylic CH), 3.70 (3H, s, OCH_3), and 1.7-3.1 (4H, m, allylic CH); mass spectrum, m/e (rel. intensity), 286 (M^+, 64), 227 (41), 183 (48), 182 (39), 181 (70), 165 (100), 162 (36), 157 (32), 155 (43), 153 (57), 152 (56), 141 (42), 128 (36), 115 (50), 105 (29), 104 (30), 77 (60), 76 (52), 51 (41), 45 (36), 43 (34), 41 (61), and 39 (40).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.32; H, 6.37.

In a preliminary experiment in which a solution of the ester 21b in excess butadiene was heated to 80° for 28 hr, the crude product contained (glpc, silicone SE-30 on Chromosorb P) a mixture of the starting ester 21b (82% of the mixture, ret. time 26.2 min) and the adduct 25 (18% of the mixture, 69.2 min).

Reaction of the Ketal Ester 21b with Butadiene under Acidic Conditions

A series of small-scale reactions were run in which various

mixtures of the ester 21b, butadiene, H_2O, CH_3SO_3H, and either PhH or DME as a co-solvent were heated in sealed tubes, and then cooled, mixed with $PhCH_2CH_2Ph$ as an internal standard, and analyzed by glpc (silicone SE-30 on Chromosorb P, apparatus calibrated with known mixtures of authentic samples). The retention times of the various components were: $PhCH_2CH_2Ph$, 3.5 min; ketone 24a, 5.6 min; ester 21b, 8.7 min; ketone 27, 10.4 min; and ketal 25, 18.3 min. In the presence of 1 molar equiv of H_2O and ca. 0.3 molar equiv of CH_3SO_3H, a reaction period of 24-48 hr at 80° was sufficient to convert practically all of the starting ester 21b to the ketone adduct 27 containing only small amounts of the previously described ketal 25 and the known[2a] ketone 24a (from hydrolysis and decarboxylation of keto ester 27). A collected (glpc) sample of the ketone 24a was identified with the previously described[2a] material by comparison of ir spectra and from the mass spectrum of the material: m/e (rel intensity) 184 (M^+, 100), 169 (30), 165 (38), 155 (33), 141 (41), 130 (91), 128 (55), 115 (80), 102 (87), 78 (33), 77 (64), 76 (60), 75 (36), 63 (52), 51 (80), 50 (54), 41 (34), 40 (40), and 39 (88).

In a larger scale experiment, a solution of 1.11 g (20.5 mmol) of butadiene, 465 mg (2.0 mmol) of the ester 21b, 0.035 ml (ca. 0.5 mmol) of CH_3SO_3H, and 0.035 ml (1.9 mmol) of H_2O in 1.5 ml of DME was heated to 80° for 31 hr in a sealed tube and then cooled and concentrated. Distillation of the pale orange residue in a short-path still under reduced pressure separated 313 mg of colorless liquid distillate that contained (glpc) 93% of the keto ester 27 (60% yield), 5% of the ketone 24a, and 2% of the ketal 25. This material was chromatographed on silica

gel with an Et_2O-hexane eluent to separate 208 mg (43%) of fractions of colorless liquid, $n^{25}D$ 1.5667, that contained (glpc) the pure keto ester 27; ir (CCl_4), 1745 (ester C=O) and 1718 cm^{-1} (C=O); uv max (95% EtOH), 248 nm (ε 11,600), 292 nm (shoulder, ε 2160), and 296 nm (ε 2210); nmr ($CDCl_3$), δ 7.2-7.9 (4H, m, aryl CH), 5.6-6.0 (2H, m, vinyl CH). 3.8-4.2 (1H, m, benzylic CH), 3.65 (3H, s, OCH_3), and 2.3-2.8 (4H, m, allylic CH_2); mass spectrum, m/e (rel. intensity), 242 (M^+, 36), 183 (74), 182 (83), 181 (100), 165 (76), 156 (36), 155 (31), 154 (32), 153 (46), 152 (47), 128 (34), 115 (39), 77 (60), 76 (41), 75 (33), 63 (36), 51 (58), and 39 (52).

Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83. Found: C, 74.18; H, 5.84.

Reaction of the Ketal Ester 21d with Butadiene

A solution of 4.16 g (15.9 mmol) of the ketal ester 21d in 9.32 g (72 mmol) of cold (-5°) liquified butadiene was heated to 130° in a sealed tube for 48 hr. The reaction mixture was distilled in a short-path still at 0.8 mm pressure to separate 3.78 g (75%) of the adduct 28 as a viscous, pale yellow liquid, $n^{25}D$ 1.5538, that solidified on standing, mp 70.6-72.7°. Recrystallization from pentane afforded the pure ketal 28 as colorless crystals, mp 75.8-77°; ir (CCl_4), 1735 (ester C=O) and 1662 cm^{-1} (weak, C=C); uv max (95% EtOH), 218 nm (shoulder, ε 7700), 225 nm (shoulder, ε 7200), 283 nm (ε 2400), and 289 nm (shoulder, ε 2200); nmr (CCl_4), δ 6.6-7.1 (3H, m, aryl CH), 5.4-5.7 (2H, m, vinyl CH), 3.8-4.3 (5H, m, CH_2O and benzylic CH), 3.75 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), and 2.0-2.9 (4H, m, allylic CH_2); mass spectrum, m/e (rel. intensity), 316 (M^+, 88), 257 (45), 254 (71), 213 (58), 212 (42),

211 (100), 195 (65), 187 (55), 163 (58), 141 (42), 115 (53), 77 (45), and 45 (48).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.19; H, 6.42.

A solution of 328 mg (1.00 mmol) of the ketal 28 and 7 ml of aqueous 5 M HCl in 14 ml of THF and 4 ml of MeOH was stirred at 26° for 24 hr and then partitioned between H_2O and Et_2O. The organic phase was dried and concentrated to leave 331 mg of crude liquid product containing (nmr analysis) ca. 75% of the keto ester 29 and ca. 25% of the starting ketal 28. Separation on a preparative TLC plate (coated with silica gel and eluted with Et_2O-hexane, 1:6 v/v) afforded 64 mg of the starting ketal 28, 5 mg of the subsequently described ketone 31, and 200 mg of the keto ester 29 that solidified on standing, mp 70-71.5°. Recrystallization from hexane afforded 143 mg (51%) of the pure keto ester 29 as colorless prisms, mp 73.6-74.9°; ir (CCl_4), 1742 (ester C=O), 1712 (C=O), and 1620 cm^{-1} (C=C); uv max (95% EtOH), 218 nm (ε 27,200), 250 nm (ε 9800), and 323 nm (ε 3900); nmr (CCl_4), δ 7.0-7.6 (3H, m, aryl CH), 5.5-6.0 (2H, m, vinyl CH), 3.7-4.1 (4H, m, benzylic CH and a CH_3O singlet at 3.78), 3.58 (3H, s, OCH_3), and 2.3-2.7 (4H, m, allylic CH_2); mass spectrum, m/e (rel. intensity), 272 (M^+, 37), 254 (24), 213 (62), 212 (100), 211 (38), 195 (36), 187 (68), 141 (27), and 44 (38).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.51; H, 5.92.

Reaction of the Ketal 18b with Butadiene

After a solution of 4.28 g (21 mmol) of the ketal 18b in 1.86 g (34.4 mmol) of cold (-5°), liquified butadiene had been heated to 130°

in a sealed tube for 72 hr, the crude product was extracted with several portions of boiling $CHCl_3$. The extract was concentrated and distilled under reduced pressure in a short-path still to separate 4.205 g (78%) of the crude adduct 30 as a pale yellow liquid, $n^{25}D$ 1.5677, that darkened on standing; ir (CCl_4), 1660 and 1615 cm^{-1} (C=C); uv max (95% EtOH), 218 nm (ε 8800), 282 nm (ε 2650), and 289 nm (ε 2350); nmr (CCl_4), δ 6.6-7.2 (3H, m, aryl CH). 5.5-5.8 (2H, m, vinyl CH), 3.8-4.2 (4H, m, CH_2O), 3.67 (3H, s, OCH_3), and 1.8-3.4 (6H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 258 (M^+, 85), 214 (39), 213 (41), 205 (100), 204 (66), 196 (68), 161 (52), 160 (82), 149 (53), 148 (96), 77 (45), and 63 (43).

A solution of 1.30 g (5.0 mmol) of the crude ketal 30 and 12 ml of aqueous 6 M HCl in 28 ml of THF was stirred at 26° for 24 hr and then partitioned between Et_2O and H_2O. After the organic extract had been washed with aqueous $NaHCO_3$, dried, and concentrated, the residual liquid was distilled (ca. 130° at 0.2 mm) in a short-path still to separate 913 mg (85%) of the crude ketone 31, $n^{25}D$ 1.5825. The product contained (glpc, Apiezon M on Chromosorb P) mainly the ketone 31 (retention time 16.9 min) accompanied by several minor, unidentified impurities (2.6, 8.7, and 22.9 min). The ketone 31 was collected (glpc) as a yellow liquid that solidified on standing, mp 37-38.1°. Recrystallization from pentane afforded the pure ketone 31 as colorless prisms, mp 41-42.1°; ir (CCl_4), 1720, 1710 (C=O), and 1618 cm^{-1} (C=C); uv max (95% EtOH), 219 nm (ε 26,300), 249 nm (ε 8400), and 322 nm (ε 3500); nmr (CCl_4), δ 7.0-7.5 (3H, m, aryl CH), 5.6-6.0 (2H, m, vinyl CH). 3.77 (3H, s, OCH_3), 3.3-3.7 (1H, m, benzylic CH), and 1.8-3.0 (5H, m, aliphatic CH); mass

spectrum, m/e (rel. intensity), 214 (M^+, 39), 161 (12), 160 (100), 145 (15), and 51 (14).

Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.38; H, 6.59.

To estimate the relative rates of reaction of the methoxyindenes 18b and 21d with butadiene, 0.92-0.98 mmol samples of these indenes were dissolved in 7.76 g (143 mmol) portions of cold (-5°) liquid butadiene and heated to 130° in sealed tubes for 8.5 hr or 12 hr. After the tubes had been cooled and opened the crude product was dissolved in $CHCl_3$, concentrated, and extracted with several portions of boiling EtOH to separate the reactants 18b and 21d and products 28 and 30 from polymeric butadiene that was insoluble in EtOH. The EtOH extracts were diluted with EtOH to a known volume and subjected to uv analysis to measure the proportions of 18b to 30 (using uv absorption at 317 nm) or 21d to 28 (using absorption at 343 nm). After a reaction period of 8.5 hr, the amounts of unchanged indenes remaining were 62% of 18b and 40% of 21d; after 12 hr, the values were 40% of 18b and 23% of 21d. Consequently, we estimate that indene ester 21d reacts with butadiene at 130° about twice as fast as the indene 18b.

References and Notes

1. (a) H. O. House, C. B. Hudson, and E. J. Racah, J. Org. Chem., 37, 989 (1972); H. O. House, J. K. Larson, and H. C. Muller, Ibid., 33, 961 (1968).

2. For examples, see (a) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, J. Am. Chem. Soc., 82, 1452, 1457 (1960); (b) H. O. House and G. H. Rasmusson, J. Org. Chem., 28, 31 (1963); (c) H. O. House and R. G. Carlson, Ibid., 29, 74 (1964); (d) G. Jammaer, H. Martens, and G. Hoornaert, Tetrahedron, 31, 2293 (1975).

3. Unpublished work from the laboratories of Dr. H. O. House by Dr. Christopher B. Hudson.

4. H. O. House and C. B. Hudson, J. Org. Chem., 35, 647 (1970).

5. H. O. House, C. B. Hudson, and E. J. Racah, J. Org. Chem., 37, 989 (1972).

6. Related procedures for the bromination of ketals include: (a) P. E. Eaton, J. Am. Chem. Soc., 84, 2344 (1962); (b) W. S. Johnson, J. D. Bass, and K. L. Williamson, Tetrahedron, 19, 861 (1963); (c) E. W. Garbisch, J. Org. Chem., 30, 2109 (1965); (d) N. B. Chapman, J. M. Key, and K. J. Toyne, Ibid., 35, 3860 (1970).

7. For related examples, see (a) J. Ficini and J. C. Depezay, Tetrahedron Lett., 937 (1968); (b) M. J. Manning, P. W. Raynolds, and J. S. Swenton, J. Am. Chem. Soc., 98, 5008 (1976).

8. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin-Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 mHz with a Varian, Model A-60 or Model T-60-A, nmr spectrometer and the 13C nmr spectra were determined at 25 mHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer), Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

9. C. F. H. Allen and F. W. Spangler, Org. Syntheses, Coll. Vol. 3, 377 (1955).

10. H. O. House and J. K. Larson, J. Org. Chem., 33, 448 (1968).

11. X. A. Dominguez, I. C. Lopez, and R. Franco, J. Org. Chem., 26, 1625 (1961).

12. R. Robinson and J. Shinoda, J. Chem. Soc., 127, 1973 (1925).

13. W. S. Johnson and W. E. Shelberg, J. Am. Chem. Soc., 67, 1853 (1945).

14. The procedure of P. E. Eaton and H. Mueller, J. Am, Chem. Soc., 94, 1014 (1972).

15. The procedure of K. L. Rinehart and D. H. Gustafson, J. Org. Chem., 25, 1836 (1960).

CHAPTER III

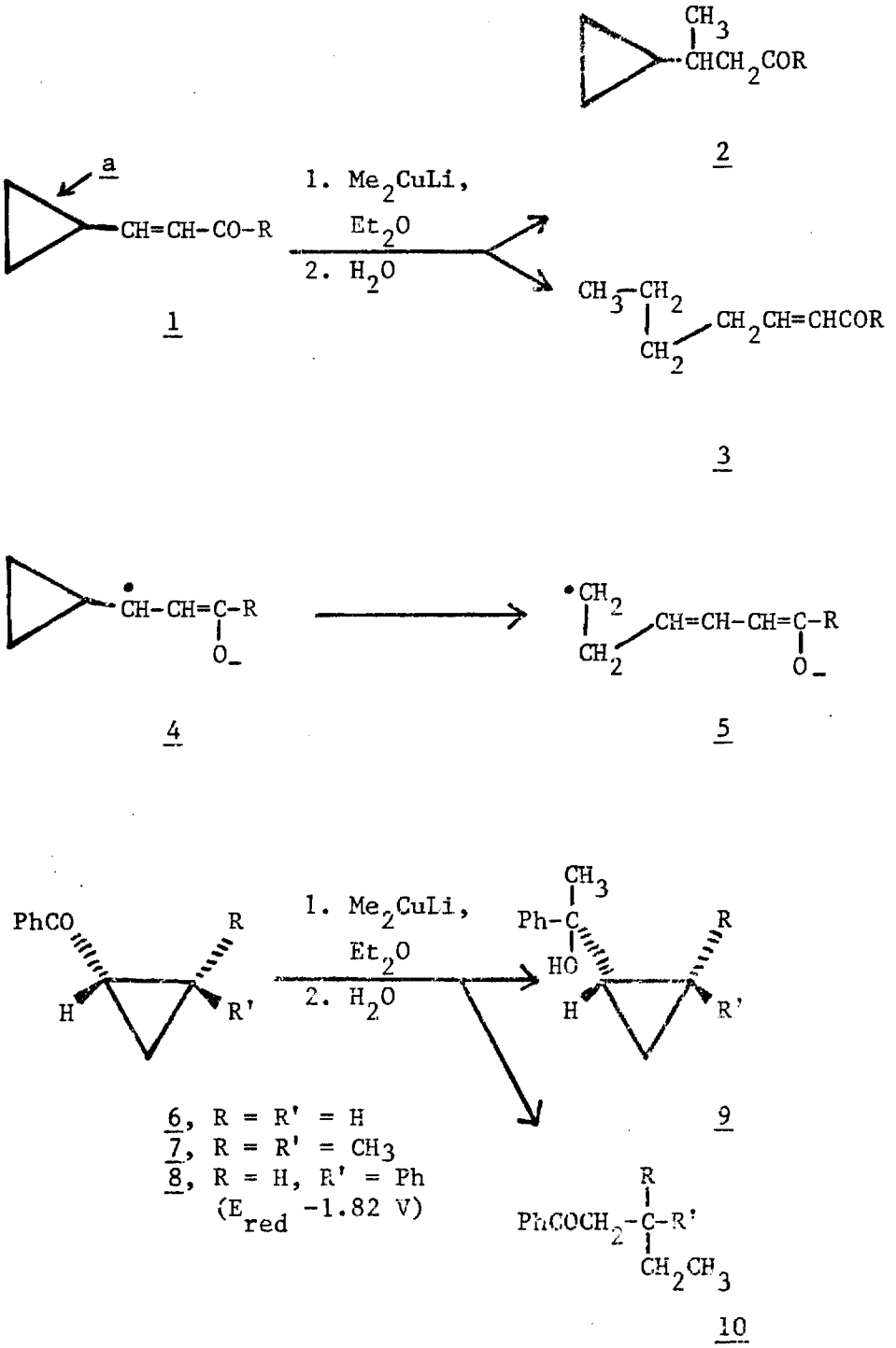
OPENING OF A CYCLOPROPYL KETONE THAT IS PART OF AN INDANONE SYSTEM

Discussion

A number of β-cyclopropyl enones 1 (Scheme I) react normally with Me_2CuLi and other cuprate reagents to form the conjugate adducts 2. However, when special structural features hold the cyclopropyl bond a (structure 1) approximately perpendicular to a plane of the enone system then an alternative reaction path involving formation of a ring-opened product 3 becomes either a significant competing reaction or the dominant reaction.[1] This ring-opening reaction 1 → 3 appears to predominate only in those cases where rearrangement of the intermediate enone anion radical 4 to the ring-opened radical 5 is relatively fast (half-life of 4 is 10^{-3} sec or less); a geometry with bond a (structure 1) perpendicular to the enone system is of course favorable to this anion radical rearrangement 4 → 5.

In a related study of the reaction of Me_2CuLi with the aryl cyclopropyl ketones 6 - 8 (all of which have reduction potentials in the range -1.8 to -2.1 V vs SCE),[2] the major product was invariably the 1,2-adduct 9 with only minor amounts (0.6 - 3.5%) of ring opened products 10. Electrochemical reduction[2] of the ketones 6 and 7 in an aprotic medium formed relatively stable anion radicals (half-lives 4-5 sec). A much less stable anion radical 11 (half-life 0.005 sec) was formed from the ketone 8 with a phenyl substituent that could stabilize

SCHEME I



1

2

3

4

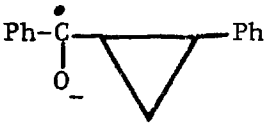
5

6, R = R' = H
7, R = R' = CH_3
8, R = H, R' = Ph
(E_{red} -1.82 V)

9

10

SCHEME I (CONTINUED)



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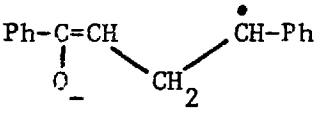

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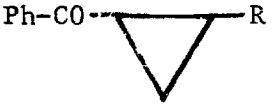
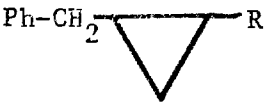


13, R = H or alkyl
14, R = CO-Ph



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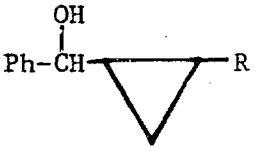

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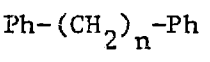
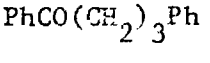


17 n = 4 or 5

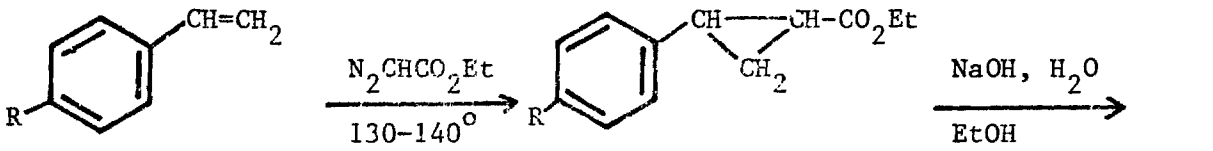


18

the rearranged anion radical 12. In keeping with these relative radical stabilities, both reduction of various cyclopropyl ketones 13 with Li or Na in NH_3[3] and electrochemical reduction of ketone 6 in aqueous EtOH[4] formed products (15, 16, and the corresponding pinacol) with the cyclopropyl ring intact. In contrast, the cyclopropyl ring was opened in the electrochemical reduction of ketone 8 to form ketone 18[4] and in the reduction of ketones 8 and 14 with Na in NH_3 to form hydrocarbons 17.[3a] However, the structures of the ring-opened products 10 (attack at the less substituted cyclopropane C atom) formed in the cuprate reactions all corresponded to the result expected from an S_N2 attack by the cuprate reagent rather than rebonding to a rearranged radical anion (e.g., 12) derived from the cyclopropyl ketone (e.g., 8). To explore further the question of whether any cuprate-aryl cyclopropyl ketone reaction might involve, at least in part, an initial electron transfer step to form an anion radical (e.g., 11), we wished to examine the cuprate reaction with a cyclopropyl ketone whose anion radical underwent rearrangement faster than the ketyl 11.

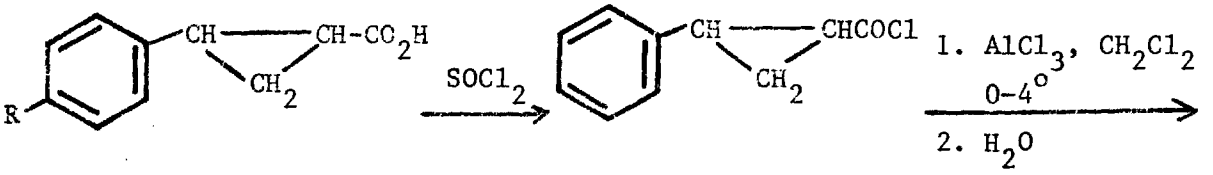
For this purpose we elected to study the fused cyclopropyl ketone 19 (Scheme II) since this molecule is held in a rigid conformation with one cyclopropyl bond (bond a in structure 19) approximately perpendicular to the plane of the carbonyl group. Our selection of this substrate was also influenced by the possibility of an efficient conversion of ketone 19 via the intermediates 20 and 21a to indanone derivatives of interest in other synthetic work.[5] Known procedures[6] were used to convert the styrenes 22 and 23 to the esters 24 and 25 (mixtures of stereoisomers) and the acids 26 and 27 (mixtures of stereoisomers). Reaction of the

SCHEME II



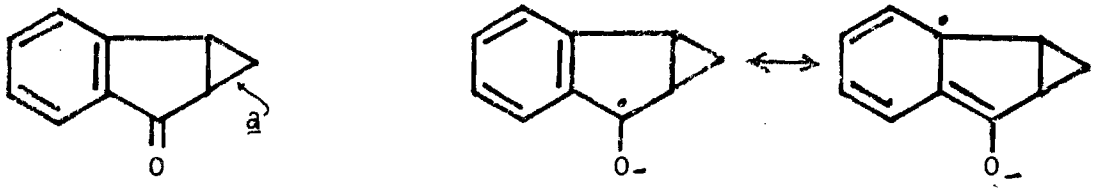
22, R = H
23, R = CH_3O

24, R = H
25, R = CH_3O



26, R = H
27, R = CH_3O

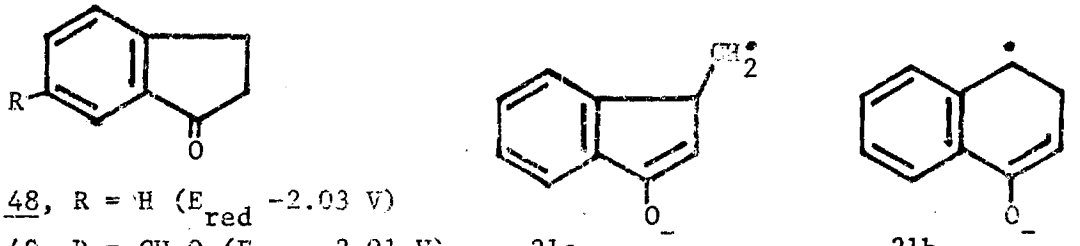
28



19, (E_{red} -2.03 V)

20

20



48, R = H (E_{red} -2.03 V)
49, R = CH_3O (E_{red} -2.01 V)

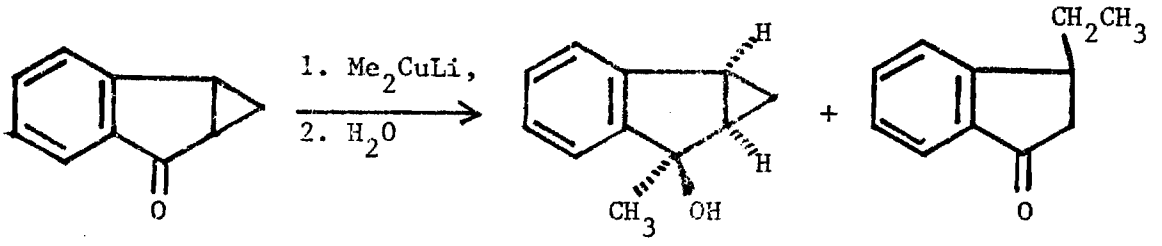
21a

21b

acid 26 (a mixture of stereoisomers) with polyphosphoric acid[6d] or, preferably, with $SOCl_2$ to form 28 followed by reaction with $AlCl_3$[7] produced the desired ketone 19. In at least the latter procedure where the ketone 19 was obtained in 61% yield, trans → cis epimerization is believed[7b] to occur during the cyclization of the acid chloride 28. Our efforts to effect the same cyclization with the methoxy acid 27 led to complex mixtures even when we employed reaction conditions that are satisfactory[5a] for the formation of the methoxyindanone 49 from the corresponding acid chloride. In view of our subsequently described results obtained with the indanone 19, other possible synthetic routes to the 6-methoxy derivative of indanone 19 were not investigated.

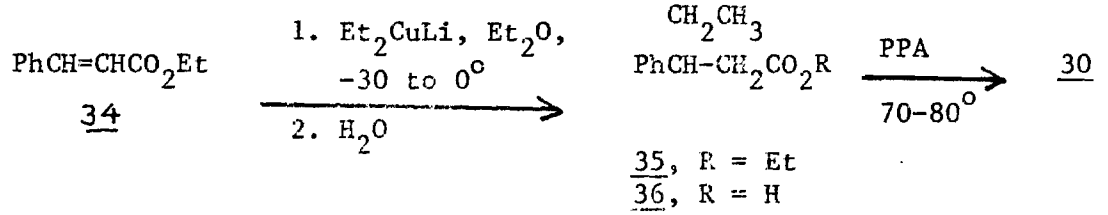
The reduction potentials[8a] of the cyclopropyl ketone 19 (E_{red} -2.03 V vs SCE) and the analogous indanone 48 (E_{red} -2.03 V vs SCE) were the same and were in a range where one-electron reduction by Me_2CuLi to form the ketyl 20 was reasonable.[9] As we had hoped, the anion radical 20 was less stable than its open chain analog 11 and had a half-life (0.001 sec) sufficiently short that a significant amount of rearrangement could occur during a cuprate reaction. In fact, reaction of the ketone 19 (Scheme III) with ethereal Me_2CuLi produced a mixture of the 1,2-adduct 29 (75-82% of the product) and a substantial amount of the ring-opened product 30 (18-25% of the product). Only the 1,2-adduct 29 was isolated from reaction of the cyclopropyl ketone 19 with MeLi. Consequently, in the cuprate reaction the proportion of ring-opened product 30 (or 10, R = H, R' = Ph) was enhanced at least 20 fold by changing the substrate from the flexible ketone 8 to the rigid system 19.

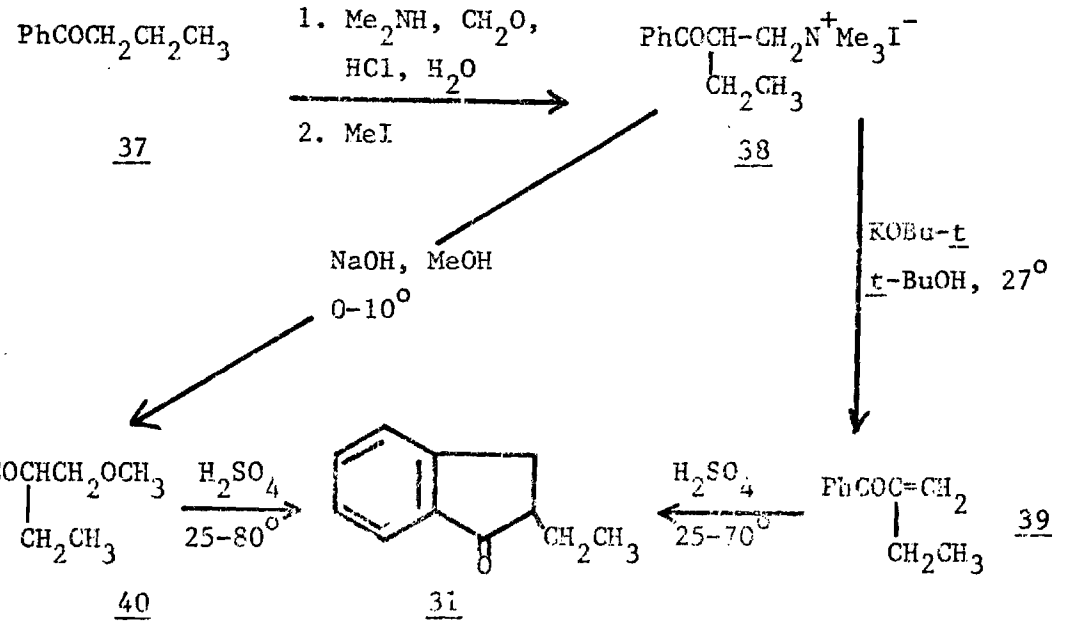
SCHEME III



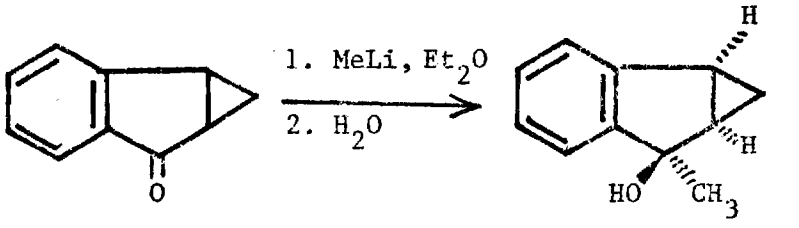
19 — 29, (39-80% yield) — 30, (13-18% yield)

+ 19 (3-20% recovery)





SCHEME III (CONTINUED)



19 29

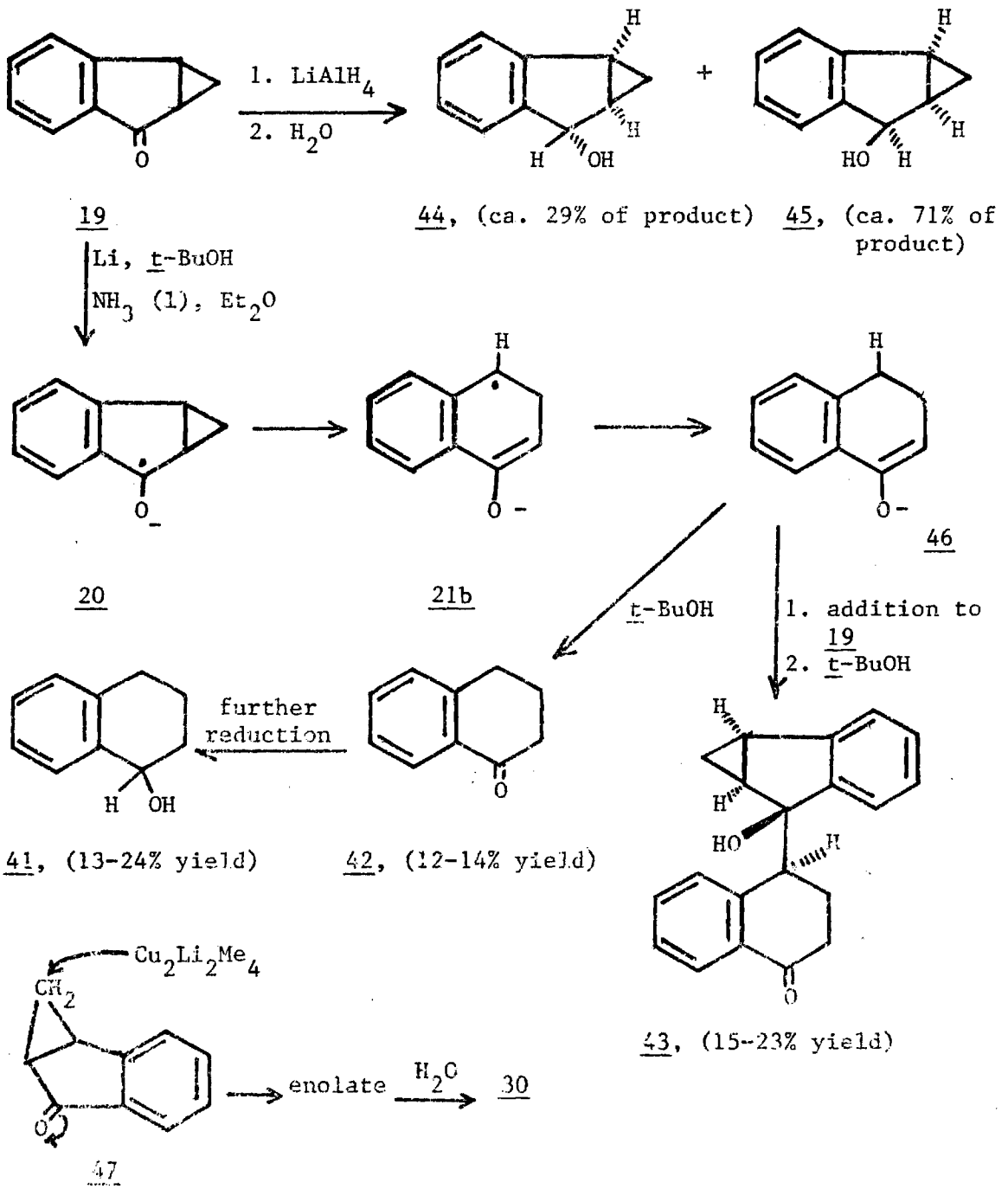
32 33

One could imagine that any one of the three cyclopropane C-C bonds in ketone 19 might be cleaved during the cuprate reaction so that any or all of the ketone products 30 - 33 might be formed. To insure that our ring-opened product was in fact the ketone 30, we obtained authentic samples of the ketones 30 - 33 and demonstrated that our product 30 contained less than 5% (if any) of the isomeric ketones 31 - 33. Authentic samples of ketones 30 and 31 were prepared by the routes indicated in Scheme III.

The foregoing results might be interpreted as reaction of the ketone 19 with Me_2CuLi to form the ketyl 20 followed by partial rearrangement to 21a and rebonding to form 29 and 30. However, such a conclusion would be warranted only if the ketyl 20 actually rearranges to the anion radical 21a (favored by the geometry of the system) rather than some other anion radical such as 21b (which allows stabilization of the radical by the adjacent phenyl ring). A clear indication that this second possibility might be correct was provided by an earlier study[10] of the reduction of ketone 19 with Li in an NH_3-Et_2O mixture. The reported products were an unidentified solid (mp 160-185°), tetralin, and tetralone.

We have repeated this reduction of ketone 19 (Scheme IV) employing a solution containing 2 molar equiv of Li and 1 molar equiv of t-BuOH in an NH_3-Et_2O mixture. The products were tetralol (41), tetralone (42), and the dihydro dimer 43 (mp 188-189.9°). Authentic samples of the alternative reduction products, the known[11,12] alcohols 44 and 45 were prepared to demonstrate their absence among the reduction products. Consideration of the products (41 - 43) formed in this metal-NH_3

SCHEME IV


1. LiAlH4
2. H2O
+
19
44, (ca. 29% of product)
45, (ca. 71% of product)
Li, t-BuOH
NH3 (l), Et2O
20
21b
46
t-BuOH
1. addition to 19
2. t-BuOH
further reduction
41, (13-24% yield)
42, (12-14% yield)
43, (15-23% yield)
Cu2Li2Me4
CH2
enolate
H2C
30
47

reduction leaves little doubt that the initally formed ketyl 20 rearranges to form anion radical 21b and not 21a. Further reduction of anion radical 21b to the dianion 46 readily accounts for all of the isolated products 41 - 43. In view of this, we conclude that reaction of the ketone 19 with Me_2CuLi to form ketone 30 does not involve the intermedaite ketyl 20 since this latter intermediate should have rearranged to 21b and then formed ketone 32. Instead, the reaction with the cuprate to form ketone 30 must again be an example of an S_N2 ring opening (see structure 47) in which the geometry of the substrate is especially favorable for attack at the cyclopropyl CH_2 group to displace an enolate anion. In agreement with this conclusion, the yield of ketone 30 from reaction of Me_2CuLi with ketone 19 was increased (see Table 3) by the addition of good donor solvents (DME or THF). In reactions of cuprates with ketones where an initial electron transfer step is involved, the presence of good donor solvents normally retards or inhibits the reaction.[12]

The structure of the dihydro dimer 43, determined by a single crystal x-ray diffraction study,[8b] is shown in Figure 1. The bond lengths and bond angles obtained from the structural determination are listed in Table 1.

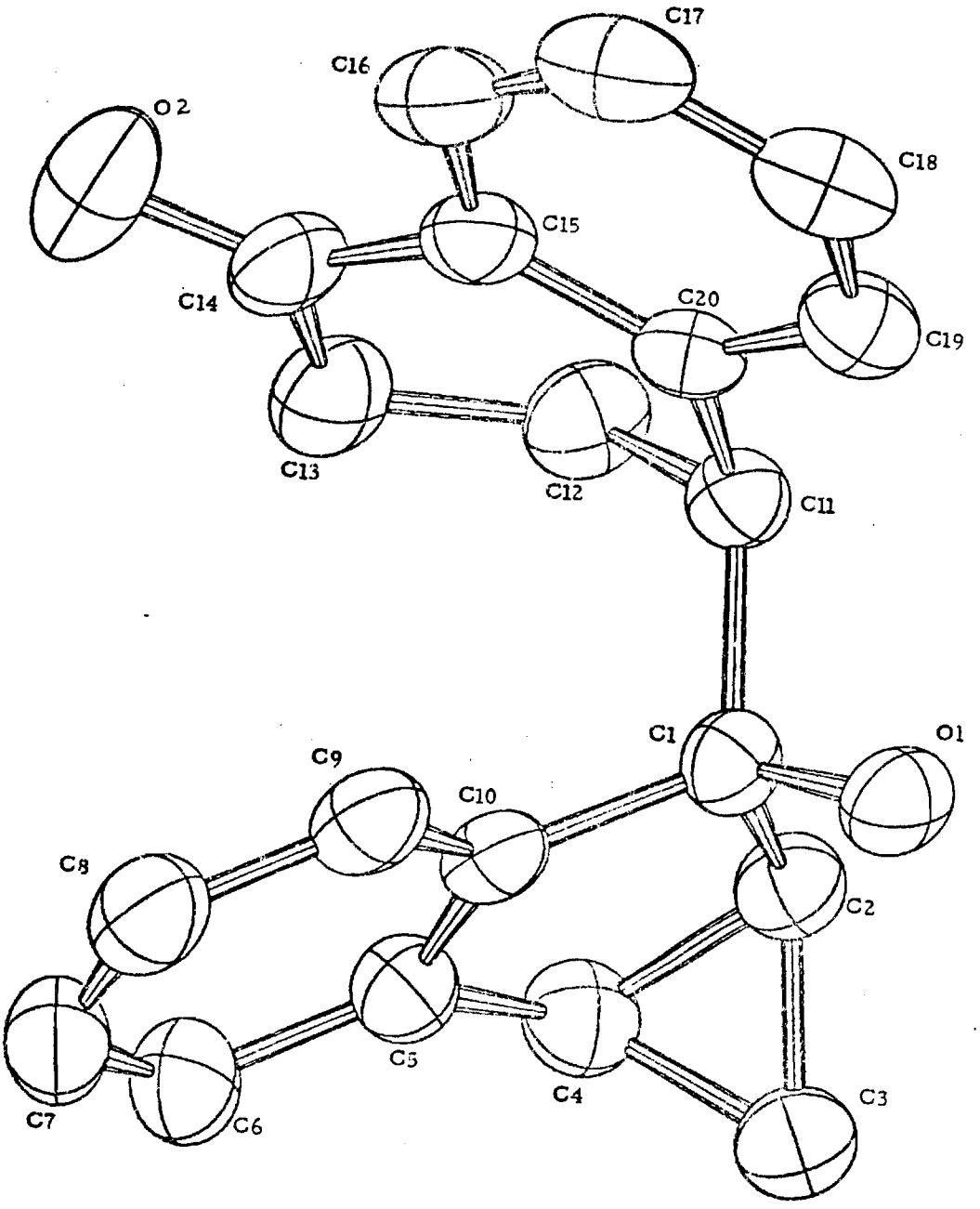


Figure 1. A Perspective View of the Molecular Structure of the Dihydro Dimer 43.

Table 1. Molecular Geometry of the Dihydro Dimer 43

(a) Bond Lengths

Atoms	Distance, A (standard deviation)	Atoms	Distance, A (standard deviation)
C1-O1	1.437 (3)	C11-C1	1.557 (4)
C1-C2	1.520 (3)	C11-C12	1.538 (4)
C2-C3	1.497 (4)	C11-C20	1.514 (4)
C2-C4	1.506 (4)	C12-C13	1.525 (4)
C3-C4	1.511 (4)	C13-C14	1.492 (4)
C4-C5	1.493 (4)	C14-O2	1.232 (3)
C5-C6	1.381 (4)	C14-C15	1.478 (4)
C5-C10	1.394 (3)	C15-C16	1.401 (4)
C6-C7	1.391 (4)	C16-C17	1.374 (4)
C7-C8	1.382 (4)	C17-C18	1.392 (4)
C8-C9	1.388 (4)	C18-C19	1.380 (4)
C9-C10	1.387 (3)	C19-C20	1.391 (3)
C10-C1	1.516 (3)	C20-C15	1.405 (4)

(b) Bond Angles

Atoms	Angle, ° (standard deviation)	Atoms	Angle, ° (standard deviation)
O1-C1-C2	113.1 (2)	C9-C10-C1	128.2 (2)
O1-C1-C10	111.7 (2)	C10-C1-C2	103.4 (2)
O1-C1-C11	105.1 (2)	C11-C1-C2	114.7 (2)
C1-C2-C3	119.0 (2)	C11-C12-C13	113.9 (2)
C1-C2-C4	108.8 (2)	C11-C20-C19	120.1 (2)
C2-C3-C4	60.1 (2)	C12-C11-C1	114.2 (2)
C2-C4-C3	59.5 (2)	C12-C13-C14	113.8 (2)
C2-C4-C5	105.6 (2)	C13-C14-C15	118.4 (2)

Table 1 (concluded)

(b) Bond Angles (cont.)

Atoms	Angle, ° (standard deviation)	Atoms	Angle, ° (standard deviation)
C2-C1-C11	109.1 (2)	C13-C14-O2	120.9 (3)
C3-C2-C4	60.4 (2)	C14-C15-C16	118.4 (2)
C3-C4-C5	113.4 (2)	C15-C14-O2	120.8 (3)
C4-C5-C6	129.3 (2)	C15-C16-C17	120.8 (3)
C4-C5-C10	110.1 (2)	C15-C20-C11	121.6 (2)
C5-C6-C7	118.6 (3)	C15-C20-C19	118.2 (2)
C5-C10-C1	111.2 (2)	C16-C17-C18	119.5 (2)
C5-C10-C9	120.5 (2)	C19-C18-C17	120.2 (3)
C6-C5-C10	120.5 (2)	C20-C11-C1	114.4 (2)
C6-C7-C8	121.0 (2)	C20-C11-C12	110.3 (2)
C7-C8-C9	120.5 (2)	C20-C15-C14	121.6 (2)
C8-C9-C10	118.8 (2)	C20-C15-C16	119.9 (2)
		C20-C19-C18	121.4 (2)

Experimental Section[13]

Preparation of the Acid Derivatives 24, 26, and 28

A cold (0°) solution of 28.53 g (0.25 mol) of N_2CHCO_2Et[14] in 26.04 g (0.25 mol) of styrene (22) was added, dropwise and with stirring during 15 min, to 13.02 g, (0.125 mol) of styrene (22) that was maintained at 130-140° under an N_2 atmosphere. The resulting mixture was stirred at 130-135° for 24 hr and then distilled to spearate 4.89 g forerun (mainly $PhCH=CH_2$) followed by 36.93 g of the crude ester 24 as a pale yellow liquid, bp 80-90° (0.15 mm), $n^{25}D$ 1.5182. Redistillation afforded 34.28 g (72%) of the ester 24 (a mixture of stereoisomers) as a colorless liquid, bp 80.5-82° (0.14 mm), $n^{25}D$ 1.5182 (lit. bp 103-105° (0.5-0.7 mm),[7a] $n^{20}D$ 1.518[7d]); ir (CCl_4), 1725 cm^{-1} (ester C=O); uv (95% EtOH) intense end absorption with a series of weak maxima (ε 251-472) in the region 253-273 nm; nmr (CCl_4, δ 6.8-7.4 (5H, m, aryl CH), 4.10 and 3.81 (2H, overlapping quartets, J = 7 Hz, CH_2O), and 0.7-2.7 (7H, m, ethoxyl CH_3 and cyclopropyl CH and CH_2); mass spectrum, m/e (rel. intensity), 190 (M^+, 29), 145 (21), 144 (18), 117 (100), 116 (23), 115 (50), and 91 (22).

Saponification of 32.64 g (172 mmol) of the ester 24 with a refluxing solution of 10.35 g (259 mmol) of NaOH and 15 ml of H_2O in 100 ml of EtOH for 24 hr followed by the usual isolation procedure yielded the crude acid 26 (a mixture of stereoisomers) as a cream-colored solid, mp 68-73° (lit.[6c] mp 55-63°). Recrystallization from H_2O afforded the mixture of stereoisomeric acids 26 in 57% yield as colorless crystals, mp 62.5-101° (lit.[6a] mp 93° (trans-isomer) and 106-107° (cis-isomer)). This crude acid (8.11 g, 50 mmol) was dissolved in 17.85 g (150 mmol) of warm $SOCl_2$ and then stirred at 25° for 24 hr, concentrated, and distilled. The acid chloride 28 (a mixture of stereoisomers) was collected as

8.69 g (96%) of pale yellow liquid, bp 126-128° (24 mm), n^{25}_D 1.5548-1.5551 (lit. bp 108-110° (2.1 mm),[6a] 120° (10 mm)[6c]); ir (CCl_4), 1780 cm^{-1} (C=O); nmr (CCl_4), δ 6.7-7.6 (5H, m, aryl CH) and 1.2-3.0 (4H, m, CH and CH_2); mass spectrum, m/e (rel. intensity), 182 (M^+, <1), 180 (M^+, 3), 145 (79), 127 (48), 125 (48), 117 (89), 116 (70), 115 (99), 91 (58), 55 (100), and 39 (37).

Preparation of the Ketone 19

A solution of 24.33 g (150 mmol) of the acid chloride 28 in 40 ml of CH_2Cl_2 was added, dropwise and with stirring during 1 hr, to a cold (0-3°) mixture of 26.0 g (195 mmol) of anhydrous $AlCl_3$ and 40 ml CH_2Cl_2. After the resulting mixture had been stirred at 0-4° for 24 hr, it was poured into ice water, acidified with HCl, and extracted with CH_2Cl_2. The organic layer was stirred for 24 hr with aqueous Na_2CO_3 and then separated, dried, and concentrated. Distillatin of the residual brown liquid (23.5 g) afforded 13.28 g (61%) of the ketone 19 as a colorless liquid, bp 77-85° (0.15-0.20 mm), n^{25}_D 1.5850-1.5855 (lit.[15] bp 80° (0.4mm)); ir (CCl_4), 1720 cm^{-1} (C=O); uv max (95% EtOH), 255 nm (ε 6450) and 298 nm (ε 1530) with a shoulder at 305 nm (ε 1360); nmr (CCl_4), δ 6.8-7.5 (4H, M, aryl CH), 2.1-3.0 (2H, m, cyclopropyl CH), and 1.0-1.7 (2H, m, cyclopropyl CH_2); mass spectrum, m/e (rel. intensity), 144 (M^+, 68), 117 (13), 116 (72), 115 (100), 89 (14), and 63 (15).

In an alternative preparation, a mixture of 27.83 g (146 mmol) of the acid 26 (a mixture of stereoisomers) and 300 g of polyphosphoric acid was stirred at 40-65° for 1.5 hr and then poured into ice water and extracted with Et_2O. After the ethereal extract had been dried and concentrated, distillation of the residual amber liquid (13.7 g) afforded

4.79 g (23%) of the ketone 19, bp 74-78° (0.1 mm), $n^{25}D$ 1.5841 - 1.5847.

Preparation of the Alcohol 29

To a cold (0°) solution of 1.442 g (10.0 mmol) of the ketone 19 in 50 ml of Et_2O was added, dropwise and with stirring during 5 min, 12 ml of an Et_2O solution containing 12 mmol of MeLi. After the resulting solution had been stirred at 25° for 10 min, it was partitioned between H_2O and Et_2O. The organic layer was dried and concentrated to leave 1.52 g (95%) of the crude alcohol 29 as a colorless liquid that solidified on standing, mp 47.9-52.6°. One recrystallization from pentane sharpened the melting point to 50-52.4° and an additional recrystallization gave 384 mg of the pure alcohol 29 as colorless plates, mp 53.8-54.2°; ir (CCl_4), 3590 and 3460 cm^{-1} (OH); uv max (95% EtOH), 264 nm (ε 682), 270 nm (ε 891), 277.5 nm (ε 800), 296 nm (ε 136), and 307 nm (ε 109); nmr ($CDCl_3$), δ 6.9-7.4 (4H, m, aryl CH), 1.3-2.5 (6H, m, cyclopropyl CH, OH, and a CH_3 singlet at 1.52), and 0.2-1.1 (2H, m, cyclopropyl CH_2); mass spectrum, m/e (rel. intensity), 160 (M^+, 14), 146 (24), 145 (99), 141 (24), 128 (31), 127 (45), 118 (28), 117 (100), 116 (45), 115 (59), and 91 (24).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.49; H, 7.59.

Reaction of the Ketone 19 with Me_2CuLi

A solution of 434 mg (3.00 mmol) of the ketone 19 in 2 ml of Et_2O was added, dropwise and with stirring during 2 min, to a cold (0°) solution of Me_2CuLi from 926 mg (4.5 mmol) of Me_2SCuBr, 9.0 mmol of MeLi (halide-free), 9 ml of Me_2S, and 21 ml of Et_2O. As the resulting orange solution was slowly warmed from 0°, a yellow precipitate began to separate

at about 10°. The mixture was stirred at 10° for 15 min and at 25° for 1 hr and then partitioned between Et_2O and an aqueous solution of NH_4Cl and NH_3. After the organic solution had been dried and concentrated, the residual green liquid (470 mg) was subjected to a preparative tlc separation on silica gel with an Et_2O-hexane mixture (1:5 v/v) as eluent. The components separated were 61 mg (13%) of the ketone 30 (R_f 0.49, 72 mg (17%) of the starting ketone 19 (R_f 0.36), and 188 mg (39%) of the alcohol 29 (R_f 0.17). The alcohol 29 and the ketone 19 were identified with previously described samples by comparison of nmr and ir spectra and tlc R_f values. The crude ketone 30 was distilled in a short-path still (ca. 100° at 0.15 mm) to separate 42 mg of the pure ketone 30 as a colorless liquid, $\underline{n}^{25}\underline{D}$ 1.5477; that was identified with a subsequently described sample by comparison of glpc retention time and ir, nmr, and mass spectra.

The following experiment was performed to demonstrate the absence of ketones 31, 32, and 33 in the reaction product. To a cold (-5 to 0°) solution of Me_2CuLi, form 1.26 g (6.13 mmol) of Me_2SCuBr, 12.0 mmol of MeLi, 6 ml of Et_2O, and 15 ml of THF, was added a solution of 428 mg (2.97 mmol) of the ketone 19 in 2.0 ml of THF. After the mixture had been stirred for 1 hr at -5 to 0° and for 5 hr at 25°, the previously described isolation procedure separated 431 mg of crude liquid product. One-half of this product was mixed with 147 mg of $PhCH_2CH_2Ph$ (an internal standard) and subjected to glpc analysis (silicone SE-52 on Chromosorb P, apparatus calibrated with known mixtures). The calculated yields were 24% of ketone 19, 31% of alcohol 29, and 19% of ketone 30. The glpc retention times for the various possible components on three different

glpc columns are summarized in Table 2. Under these glpc conditions, samples of the alcohol 29 gave a single broad glpc peak as indicated in Table 2. However, samples of this peak collected from the glpc apparatus had ir (1645 cm^{-1}, C=C) and mass spectra (M^+, at m/e 142) corresponding to one or more dehydration products from the alcohol 29. Since the glpc response factor for this peak was relatively constant, this peak was used to estimate the yield of the alcohol 29 formed with the realization that some uncertainty in the yield of alcohol 29 may result from this analytical procedure. The second half of the crude reaction product was subjected to glpc analysis (silicone QF-1 on Chromosorb P) to demonstrate the absence of ketones 31 and 33. When authentic samples of thses ketones 31 and 33 were added to aliquots of the crude product in amounts corresponding to 5% of the amount of ketone 30 present, each ketone 31 or 33 was easily detected. The glpc peak (silicone QF-1 on Chromosorb P) corresponding in retention time to either ketone 30 or ketone 32 was collected; after short-path distillation, one portion of this collected sample was identified with an authentic sample of ketone 30 by comparison of ir spectra. A second portion of the collected sample was analyzed on a third glpc column (UCON 50-HB on Chromosorb P) to demonstrate the absence of ketone 32. When a synthetic mixture of 5% of ketone 32 and 95% of ketone 30 was subjected to this same analytical procedure, the minor constituent, ketone 32, was readily detected. Thus, we have found no evidence indicating the presence of any of the ketones 31, 32, or 33 in the crude product and can conclude that more than 95% of the ketonic product formed in this reaction is 3-ethylindanone (30).

Table 2. GLPC Retention Times for Various Possible Components in the Mixture From Reaction of Ketone 19 with Me_2CuLi

Compound	GLPC Retention Time (min) Silicone SE-52, 176°	Silicone QF-1, 150°	UCON 50-HB, 217°
ketone 19	8.3	21.0	--
ketone 30	9.8[a]	23.9[b]	62.7
ketone 32	10.6[a]	23.8[b]	68.2
ketone 31	--	18.0[c]	--
ketone 33	9.6[a]	18.3[c]	--
alcohol 29	5.1[d]	5.2-11.0 (broad)	--
$PhCH_2CH_2Ph$	14.0	13.5	--

[a]Ketones 30, 32, and 33 are not resolved. [b]Ketones 30 and 32 are not resolved. [c]Ketones 31 and 33 are not resolved. [d]This peak contains one or more dehydration products from the alcohol 29.

In an additional series of experiments, colorless solutions of Me_2CuLi (containing a very small amount of yellow $(MeCu)_n$ precipitate to ensure the absence of excess MeLi), prepared from 6.0 mmol of Me_2SCuBr, 12 mmol of MeLi (halide free), and 6 ml of Et_2O, were diluted with the solvents indicated in Table 3 and then 3.0 mmol of the ketone 19 was added, dropwise and with stirring during 1-5 min at the initial reaction temperature indicated in Table 3. After the reaction mixtures had been stirred and allowed to warm to 25° during the times indicated in Table 3, they were siphoned into an aqueous solution of NH_4Cl and NH_3 and then extracted with Et_2O. The ethereal extracts were mixed with a known weight of $PhCH_2CH_2Ph$, dried, and subjected to glpc analysis (silicone SE-52 on Chromosorb P at 176°, apparatus calibrated with known mixtures). The yields of the various products 19, 29, and 30 are summarized in Table 3.

Sources of Ketones 48, 49, 31-33, and 39

The preparation and properties of indanones 48 and 49 are described elsewhere[5c] and authentic samples of tetralones 32 and 33 were obtained from Aldrich Chemical Co., Inc. A sample of the tetralone 32, purified by short path distillation, was obtained as a colorless liquid, $n^{25}D$ 1.5597 (lit.[16] bp 133-134° (12 mm), $n^{19}D$ 1.5620); ir (CCl_4), 1691 cm^{-1} (C=O); uv max (95% EtOH), 212 nm (ε 9840), 249 nm (ε 10,200), and 293 nm (ε 1700); nmr (CCl_4), δ 6.6-7.9 (4H, m, aryl CH) and 0.9-3.3 (8H, m, aliphatic CH including a CH_3 doublet, J = 6.5 Hz, at 1.28); mass spectrum, m/e (rel. intensity), 160 (M^+, 100), 145 (67), 132 (66), 118 (64), 117 (32), 115 (23), 104 (58), 77 (21), and 51 (22). Purification by short-path distillation afforded a sample of the tetralone 33 as a colorless

Table 3. Reaction of Ketone 19 with Me_2CuLi in Various Solvents

Solvents (ml)	Initial Reaction temperature, °C	Reaction time, hr	YIELDS % ketone 19	ketone 30	alcohol 29
Et_2O (14) + Me_2S (9)	5-15°	1	3-20	17-18	62-80
Et_2O (5-7) + pentane (17-22)	5-15°	1.5-17	1-6	6-7	87-92
Et_2O (6) + THF (17)	5°	18	13	27	60
Et_2O (6) + DME (17-27)	5-15°	17-18	28-36	18-21	40-47

liquid, $n^{25}D$ 1.5523 (lit.[17] bp 136-138° (16 mm), $n^{25}D$ 1.5538); ir (CCl_4), 1692 cm^{-1} (C=O); uv max (95% EtOH), 210 nm (ε 14,200), 247.5 nm (ε 11,400), and 292 nm (ε 1540); nmr (CCl_4). δ 7.0-8.2 (4H, m, aryl CH), 1.4-3.2 (5H, m, aliphatic CH), and 1.17 (3H, d, J = 6 Hz, CH_3); mass spectrum, m/e (rel. intensity), 161 (39), 160 (M^+, 92), 145 (76), 142 (39), 141 (33), 132 (42), 131 (65), 119 (49), 118 (100), 117 (36), 115 (37), 91 (37), 90 (68), 89 (42), and 77 (34). A previously described procedure[18] was used to convert $PhCOCH_2CH_2CH_3$ to the methiodide 38 of its Mannich base. A solution of KOBu-t, from 0.49 g (12.5 mg-atom) of K and 25 ml t-BuOH, was added, dropwise and with stirring during 5 min, to a suspension of 4.34 g (12.5 mmol) of the ammonium salt 38 in 25 ml of t-BuOH. The resulting solution was stirred at 25-27° for 10 min and then partitioned between H_2O and Et_2O. After the ethereal layer had been dried and concentrated, distillation of the residual liquid separated 1.13 g (56%) of the pure (glpc analysis) unsaturated ketone 39, bp 58-60° (0.15 mm), $n^{25}D$ 1.5294 - 1.5299, accompanied by 267 mg of less pure ketone 39, bp 64-67° (0.15 mm), $n^{25}D$ 1.5275 (lit.[18] bp 49-50 (0.15 mm), $n^{25}D$ 1.5300); ir (CCl_4), 1660 (C=O), 1625 (C=C), and 980 cm^{-1} ($C=CH_2$); uv max (95% EtOH), 246 nm (ε 9510), 335.5 nm (ε 93); nmr (CCl_4), δ 6.9-7.6 (5H, m, aryl CH), 5.5-5.6 (1H, m, vinyl CH), 5.2-5.4 (1H, m, vinyl CH), 2.38 (2H, q, J = 7 Hz, CH_2), and 1.06 (3H, t, J = 7 Hz, CH_3); mass spectrum, m/e (rel. intensity), 160 (M^+, 20), 145 (15), 105 (100), 77 (52), and 51 (17). The previously described[19] cyclization was effected by adding 974 mg (6.1 mmol) of the unsaturated ketone 39, dropwise and with stirring during 1 min, to 4.0 ml of conc. H_2SO_4. The resulting solution, whose temperature initially rose to 70°, was stirred and

allowed to cool for 90 min and then poured onto ice and partitioned between H_2O and Et_2O. The Et_2O solution was washed with aqueous $NaHCO_3$, dried, and concentrated to leave a crude yellow liquid product containing (glpc, silicone SE-30 on Chromosorb P) the indanone 31 (ret. time 24.6 min) but lacking peaks corresponding to the enone 39 (15.9 min) or the subsequently described methoxy ketone 40 (29.1 min). Distillation afforded 866 mg (89%) of the indanone 31 as a colorless liquid, bp 65-66° (0.05 mm), $n^{25}_{\equiv D}$ 1.5452 - 1.5456 (lit.[19] bp 143° (18 mm), $n^{31}_{\equiv D}$ 1.5420); ir (CCl_4), 1718 cm^{-1} (C=O); uv max (95% EtOH), 245 nm (ε 12,100), and 291.5 (ε 2170); nmr (CCl_4), δ 6.7-7.5 (4H, m, aryl CH), 1.1-3.5 (5H, m, CH and CH_2), and 0.91 (3H, t, J = 7 Hz, CH_3); mass spectrum, m/e (rel. intensity), 160 (M^+, 4), 133 (19), 132 (100), 131 (50), and 103 (15).

In an alternative procedure, 94 ml of aqueous 6 M NaOH (564 mmol) was added, dropwise with stirring and cooling during 30 min, to a cold (-1 to -4°) suspension of 50.3 g (171 mmol) of the methiodide 38 in 500 ml of MeOH. After the resulting mixture had been stirred at 0° for 1 hr and at 10° for 2 hr, it was partitioned between H_2O and Et_2O. After the Et_2O solution had been dried and concentrated, distillation of the residual liquid (20.92 g) afforded 19.9 g of fractions, bp 90-95° (0.14 mm), $n^{25}_{\equiv D}$ 1.5111 - 1.5145, containing (glpc) various mixtures of the enone 39 and the methoxy ketone 40. Fractions rich in the methoxy ketone 40 were redistilled to separate 3.86 g of the higher boiling pure (glpc) methoxy ketone 40, bp 114-116° (6 mm), $n^{25}_{\equiv D}$ 1.5114; ir (CCl_4), 1685 cm^{-1} (C=C); uv max (95% EtOH), 244 nm (ε 12,500), 279 nm (ε 1060), and 320 nm (ε 80); nmr (CCl_4), δ 7.2-8.1 (5H, m, aryl CH), 3.3-3.8 (3H, m, CH and CH_2O), 3.17 (3H, s, OCH_3), 1.3-1.9 (2H, m, CH_2), and 0.83 (3H, t, J = 7 Hz,

CH_3); mass spectrum, m/e (rel. intensity), 192 (M^+, 2), 163 (64), 160 (50), 137 (55), 136 (34), 106 (28), 105 (100), 77 (66), 51 (28), and 45 (45).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.00; H, 8.42.

The methoxy ketone 40 (1.92 g, 10 mmol) was added, dropwise and with stirring during 1 min, to 4.0 ml of conc. H_2SO_4. The resulting solution was warmed to 80° for 2 hr and then cooled, poured onto ice, and partitioned between H_2O and Et_2O. After the Et_2O solution had been washed with aqueous $NaHCO_3$, dried, and concentrated, the residual liquid was distilled to separate 1.34 g (84%) of the indanone 31, bp 73-74° (0.13 mm), $n^{25}D$ 1.5456.

Preparation of an Authentic Sample of the Indanone 30

A solution of 11.5 g mmol of EtLi in 14 ml of PhH and 15 ml of Et_2O was added, dropwise with stirring and cooling, to a cold (-50°) mixture of 1.88 g (5.78 mmol) of Me_2SCuBr and 5 ml of Et_2O. As the resulting mixture (unchanged Me_2SCuBr still present) was warmed to -38 to -40°, the Me_2SCuBr dissolved and a black colloidal solid (presumably Cu°) began to separate. While this cuprate reagent was kept at -25 to -30°, a solution of 782 mg (4.44 mmol) of the ester 34 in 5 ml of Et_2O was added, dropwise and with stirring during 5 min. The resulting mixture was allowed to warm to 0°, with stirring, during 30 min and then added to an aqueous solution of NH_3 and NH_4Cl and extracted with Et_2O. After the ethereal extract had been dried and concentrated, the residual liquid (1.029 g) was distilled to separate 542 mg (59%) of the ester 35 as a colorless liquid, bp 71.5-73° (0.07 mm), $n^{25}D$ 1.4878 - 1.4887; ir

(CCl_4), 1735 cm^{-1} (ester C=O); nmr (CCl_4), δ 6.8-7.2 (5H, m, aryl CH), 3.86 (2H, q, J = 7 Hz, ethoxy CH_2), 1.3-3.2 (5H, m, CH and CH_2), 1.03 (3H, t, J = 7 Hz, ethoxyl CH_3), and 0.75 (3H, t, J = 7 Hz, CH_3); mass spectrum, m/e (rel. intensity), 206 (M^+, 17), 135 (47), 132 (55), 131 (21), 119 (56), 118 (54), 117 (21), 105 (30), 91 (100), and 88 (33). The product exhibited a single glpc peak (silicone SE-52 on Chromosorb P) corresponding to the ester 35 (ret. time 17.2 min) and lacked a peak corresponding to the starting ester 34 (18.6 min).

A solution of 1.218 g. (5.9 mmol) of the ester 35, 523 mg (13.1 mmol) of NaOH, and 2 ml of H_2O in 25 ml of EtOH was refluxed for 4 hr and then partitioned between H_2O and Et_2O. This ethereal extract contained 35 mg (3%) of the unchanged ester. After the aqueous solution had been acidified (HCl) and extracted with Et_2O, the ethereal extract was dried, concentrated and distilled in a short-path still (100° and 0.5 mm) to separate 913 mg (87%) of the acid 36 as a pale yellow liquid, $n^{25}D$ 1.5173, that solidified on standing, mp 50-54.2°. Successive recrystallization from Et_2O-pentane and from pentane separated the pure acid 36 as a colorless powder, mp 59-60 (lit.[20] mp 62-64°); ir (CCl_4), 2950 (broad, associated OH) and 1713 cm^{-1} (carboxyl C=O); uv (95% EtOH), end absorption (ϵ 6580 at 210 nm) with a series of weak maxima (ϵ 73-244) in the region 237-268 nm; nmr (CCl_4), δ 11.88 (1H, s, OH), 6.8-7.5 (5H, m, aryl CH), 1.4-3.3 (5H, m, CH and CH_2), and 0.75 (3H, t, J = 7 Hz, CH_3); mass spectrum, m/e (rel. intensity), 178 (M^+, 86), 150 (29), 149 (50), 132 (25), 119 (75), 118 (69), 107 (100), 105 (39), 104 (36), 103 (42), 91 (81), 79 (32), 77 (35), and 43 (24).

The solid acid 36 (824 mg or 4.62 mmol) was dissolved in 50 g of

warm (50°) polyphosphoric acid and the resulting solution was heated to 70-80° for 2 hr and then poured into cold H_2O and extracted with Et_2O. The Et_2O solution was washed with aqueous $NaHCO_3$, dried, and concentrated to leave 780 mg of crude liquid product. Distillation in a short-path still (110-130° and 0.06 mm) separated 530 mg (72%) of the indanone 30 as a colorless liquid, $n^{25}D$ 1.5482 (lit.[21] bp 116° (10 mm)); ir (CCl_4), 1720 cm^{-1} (C=O); uv max (95% EtOH), 244.5 nm (ε 11,500), 288 nm (ε 2450), and 293 nm (ε 2480); nmr (CCl_4), δ 7.0-8.0 (4H, m, aryl CH), 1.1-3.5 (5H, m, CH and CH_2), and 0.90 (3H, t, J = 7 Hz, CH_3); mass spectrum, m/e (rel. intensity), 160 (M^+, 63), 145 (37), 133 (46), 132 (100), 131 (86), 117 (29), 115 (39), 104 (29), 103 (61), 102 (29), and 77 (39).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.35; H, 7.56.

Preparation of p-Methoxystyrene (23)

Following a previously described procedure,[22] a mixture of 50.0 g (0.28 mol) of p-methoxycinnamic acid, 5.0 g of Cu powder, and 100 ml of quinoline was heated to boiling during 40 min, and then held at the boiling point for 15 min while the volatile materials were allowed to distill from the reaction flask. The yellow liquid distillate was decanted from a small amount of the solid starting acid that had co-distilled and then partitioned between Et_2O and aqueous 6 M HCl. The ehtereal layer was dried, concentrated, and distilled to separate 20.25 g (54%) of the styrene 23 as a colorless liquid, bp 60-64° (1.7 mm), $n^{25}D$ 1.5600 - 1.5670 (lit.[22] bp 77-80° (3 mm), $n^{20}D$ 1.5609 - 1.5620); ir (CCl_4), 1628 (C=C) and 908 cm^{-1} ($CH=CH_2$); uv max (95% EtOH), 259 nm (ε 18,100), 292 nm (ε 2430), and 303 nm (ε 1420); nmr (CCl_4), δ 6.2-7.3

(5H, m, aryl CH and vinyl CH), 5.45 (1H, d of d, J = 1 and 17 Hz, vinyl CH), 4.98 (1H, d of d, J = 1 and 11 Hz, vinyl CH), and 3.57 (3H, s, OCH_3); mass spectrum, m/e (rel. intensity), 134 (M^+, 100), 119 (20), and 91 (20).

Preparation of the Acid Derivatives 25 and 29

A solution of 11.41 g (100 mmol) of N_2CHCO_2Et in 13.42 g (100 mmol) of the styrene 23 was added, dropwise and with stirring during 40 min, to 4.80 g (35.8 mmol) of the styrene 23 while the temperature of the mixture was maintained at 130-145°.[6b] The resulting solution was heated to 130° for an additional 12 hr during which time the color of the solution turned from orange to red to amber. The resulting mixture was fractionally distilled to separate 7.74 g of low boiling fractions, bp 38-52° (0.11-0.13 mm), n^{25}_D 1.5595 - 1.5653, containing (nmr analysis) the unchanged olefin 23. Subsequent distillation fractions contained 12.06 g (55%) of the crude ester 25 as a liquid, bp 52-145 (0.13 mm), that solidified on standing, mp 58-74°. Recrystallization from pentane separated 6.21 g of ester 25 (a mixture of cis and trans isomers) as fractions of colorless crystals melting within the range 76-83°. Repeated recrystallization from pentane afforded a sample of the trans ester 25 as colorless plates, mp 81.1-82.8° (lit.[23] mp 83-84°); ir (CCl_4), 1727 cm^{-1} (ester C=O); uv max (95% EtOH), 232 nm (ε 14,900), 279.5 nm (ε 1690), 282 nm (ε 1650), and 289 nm (shoulder, ε 1190); nmr ($CDCl_3$), δ 6.8-7.1 (4H, m, aryl CH), 4.18 (2H, q, J = 7 Hz, ethoxy CH_2), 3.75 (3H, s, OCH_3), and 0.9-2.8 (7H, m, CH_3 and cyclopropyl CH and CH_2); mass spectrum, m/e (rel. intensity), 220 (M^+, 78), 191 (46), 175 (55), 174 (32), 165 (31), 163 (30), 148 (45), 147 (100), 146 (49), 145 (49), 131 (31), 115 (37),

103 (30), and 91 (27).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.96; H, 7.32.

A solution of 3.34 g (15 mmol) of the ester 25, 1.05 g (26 mmol) of NaOH, and 2.6 ml of H_2O in 15 ml of EtOH was refluxed for 15 hr and then diluted with H_2O and distilled to remove most of the EtOH. After the resulting basic aqueous solution had been extracted with Et_2O, it was cooled, acidified (HCl), and again extracted with Et_2O. This latter ethereal extract was dried and concentrated to leave 2.72 g (93%) of the acid 27 as a white powder, mp 112.1-113.9°. Recrystallization from a $CHCl_3$-hexane mixture gave the trans-acid 27, mp 113-114° (lit. trans-acid mp 113.2-114.2°,[24] 114-114.5°,[23] cis-acid, mp 100.8-101°[24]); ir ($CHCl_3$), 2950 (broad, assoc. OH) and 1690 cm^{-1} (carboxyl C=O); uv max (95% EtOH), 231 nm (ε 14,200), 278.5 nm (ε 1650), and 281.5 nm (ε 1630); nmr (CD_3COCD_3), δ 7.83 (1H, broad, OH), 6.7-7.2 (4H, m, aryl CH), 3.76 (3H, s, OCH_3), and 1.0-2.7 (4H, m, cyclopropyl CH and CH_2); mass spectrum, m/e (rel. intensity), 192 (M^+, 57), 147 (100), 131 (32), 115 (31), 105 (36), 103 (36), 91 (36), and 77 (56).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.68; H, 6.33.

Reduction of the Ketone 19 with $LiAlH_4$

A solution of 1.44 g (10 mmol) of the ketone 19 in 20 ml of Et_2O was added, dropwise and with stirring during 5 min, to a solution of 0.57 g (15 mmol) of $LiAlH_4$ in 80 ml of Et_2O. After the resulting solution had been stirred for 25° for 24 hr, EtOAc was added to consume the excess $LiAlH_4$ and the mixture was partitioned between Et_2O and H_2O. The organic

layer was washed with aqueous NaCl, dried, and concentrated to leave 1.36 g (93%) of a waxy solid, mp 40-69°, containing (ir, nmr, and tlc analysis, silica gel coating with an EtOAc-hexane eluent, 15:85 v/v) a mixture of the alcohol 44 (ca. 29%, R_f 0.36) and the alcohol 45 (ca. 71%, R_f 0.29) but lacking ir absorption attributable to the starting ketone 19. This mixture was subjected to low-pressure liquid chromatography on silica gel with an EtOAc-hexane eluent (1:4 v/v) to separate 595 mg of early fractions containing (nmr analysis) various mixtures of alcohols 44 and 45 and 449 mg of later fractions containing alcohol 45 as colorless needles, mp 82-82.9°. Repeated chromatography of these latter fractions afforded the pure (nmr analysis) alcohol 45, mp 85.2-86° (lit.[11b] mp 85.5-87.5°); ir (CCl_4), 3574 and 3370 cm^{-1} (OH); nmr ($CDCl_3$), δ 6.8-7.5 (4H, m, aryl CH), 5.55 (1H, broad d, J = 6 Hz, OCH), 1.7-2.7 (3H, m, OH and cyclopropyl CH), 0.6-1.2 (1H, m, cyclopropyl CH), and 0.2-0.6 (1H, m, cyclopropyl CH); mass spectrum, m/e (rel. intensity), 146 (M^+, 30), 145 (26), 131 (32), 129 (25), 128 (100), 127 (27), 117 (94), 116 (82), 115 (72), 63 (27), 51 (30), and 39 (21).

The early chromatographic fractions (containing mixtures of alcohols 44 and 45) from several reactions were combined and rechromatographed to separate the alcohol 44 as a colorless oil that thus far has not crystallized (lit.[11b] mp 67-68.5°). However, the spectral properties of the sample correspond to those previously reported[11b] for alcohol 44; ir (CCl_4), 3565 and 3310 cm^{-1} (OH); nmr ($CDCl_3$), δ 6.8-7.6 (4H, m, aryl CH), 4.88 (1H, partially resolved multiplet, OCH), 1.8-2.9 (3H, m, OH and cyclopropyl CH), 0.9-1.5 (1H, m, cyclopropyl CH), and -0.1 to 0.2 (1H, m, cyclopropyl CH); mass spectrum (relative intensity) 146 (M^+, 13), 145 (25), 131 (42), 129 (27), 128

(85), 127 (29), 117 (100), 116 (42), 115 (57), 91 (28), 77 (28), 63 (33), 51 (49), 50 (24), and 39 (38).

Reduction of the Ketone 19 with Li in NH_3

To a cold (-33°) solution of 139 mg (20 mmol) of Li in 100 ml of NH_3 was added, dropwise and with stirring during 2 min, a solution of 1.44 g (10 mmol) of the ketone 19 and 740 mg (10 mmol) of t-BuOH in 20 ml of Et_2O. The resulting solution, from which the blue color was discharged as the last of the ketone solution was added, was stirred for 5 min, neutralized by the addition of excess solid NH_4Cl, and then the NH_3 was allowed to evaporate. The residue was partitioned between Et_2O and H_2O and the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual colorless semisolid (1.506 g) was triturated with Et_2O to separate several fractions of the crude dihydro dimer 43 (total 335 mg, 23%) melting within the range 181-187.5°. Concentration of the mother liquors from this separatation left 1.124 g of crude liquid product. Nmr and glpc analyses allowed us to conclude that neither tetralin nor either of the isomeric alcohols 44 or 45 was present in any significant quantity. An aliquot of this product mixture was mixed with a known weight of $PhCH_2CH_2Ph$ (an internal standard) for glpc analysis (silicone SE-30 on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained the tetralol 41 (24% yield, eluted as the corresponding olefin with ret. time 12.1 min), a mixture of the tetralone 42 and the starting ketone 19 (25.4 min, not resolved, total yield ca. 30%) and $PhCH_2CH_2Ph$ (43.5 min). Under the same glpc conditions the retention times for tetralin and the alcohols 44 and 45 (not resolved, eluted from the glpc column as naphthalene) were 11.4 min and 13.1 min and the dihydro

dimer 43 was not eluted. A 977-mg aliquot of the crude liquid product was chromatographed on silica gel with an EtOAc-hexane eluent (15:85 v/v) to separate 153 mg (12%) of early fractions containing tetralone (42, identified with an authentic sample by comparison of ir and nmr spectra) followed by 110 mg (9%) of the starting ketone 19 (identified by comparison of ir and nmr spectra). Subsequent chromatographic fractions contained 505 mg of various mixtures of the tetralol 41 and a second solid product. Further purification by preparative TLC separated 279 mg (91%) of the tetralol 41 (identified with an authentic sample by comparison of ir and nmr spectra) and 89 mg of a colorless solid, mp 148.5-149.7°, believed to be a second stereoisomer of the dihydro dimer 43; ir ($CHCl_3$), 3560, 3460 (OH), and 1670 cm^{-1} (conjugated C=O); mass spectrum, m/e (rel. intensity), 273 (20), 272 (82), 244 (74), 243 (32), 239 (22), 230 (42), 229 (45), 228 (28), 216 (40), 215 (100), 141 (29), 129 (22), 128 (73), 116 (29), 115 (76), 91 (23), 77 (23), 63 (28), 51 (28), 40 (97), and 39 (35).

In a second comparable experiment involving reduction of 1.44 g (10 mmol) of the ketone 19 with 143 mg (21 mg-atom of Li) and 740 mg (10 mmol) of t-BuOH in 20 ml of Et_2O and 100 ml of NH_3, the isolated dihydrodimer 43 (mp 182.6-187.7°) amounted to 187 mg (13%). The semisolid (1.23 g) recovered from the mother liquor exhibited tlc spots (silica gel coating, EtOAc-hexane eluent, 15:85 v/v) corresponding to tetralone 42 (R_f 0.50), the starting ketone 19 (R_f 0.40), and two (or more) more slowly eluted components (R_f 0.32 and 0.21) but lacked a spot corresponding to tetralin R_f 0.86). This mixture was subjected to low-pressure liquid chromatography (silica gel with an EtOAc-hexane eluent)

to separate early fractions containing 203 mg (14%) of tetralone (42) followed by 74 mg (5%) of the starting ketone 19. Both materials 42 and 19 were identified with authentic samples by comparison of ir and nmr spectra. Subsequent chromatographic fractions (506 mg) contained (ir and nmr analyses) mixtures of mainly tetralol (41) and the dihydro dimer 43 (or its stereoisomer) and the final fractions contained 30 mg (total yield 217 mg of 15%) of the dihydro dimer 43, mp 186-187.5°. The intermediate fractions were subjected to preparative TLC to separate 186 mg (13%) of tetralol (41) and 22 mg of a solid, mp 147.2-150°, believed to be a stereoisomer of the dihydro dimer 43. The fractions containing the tetralol (41) were distilled in a short-path still (ca. 80° at 0.15 mm) to separate the tetralol as a colorless liquid, $n^{25}D$ 1.5628. This material was identified with an authentic sample by comparison of ir and nmr spectra.

The dihydro dimer crystallized from a $CHCl_3$-hexane mixture as colorless needles, mp 188-189.9°; ir ($CHCl_3$), 3562, 3390 (OH), and 1675 cm^{-1} (conj. C=O); uv max (95% EtOH), 251.5 nm (ε 10,600), 279.5 nm (ε 1760), and 297 nm (ε 1680); nmr ($CDCl_3$), δ 6.7-8.2 (7H, m, aryl CH), 6.1-6.4 (1H, m, aryl CH), 3.3-3.6 (1H, m, benzylic CH), 1.4-2.9 (7H, m, aliphatic CH and OH), 0.8-1.4 (1H, m, cyclopropyl CH), and 0.2-0.7 (1H, m, cyclopropyl CH); mass spectrum, m/e (rel. intensity), 290 (M^+, 0.4), 147 (11), 146 (100), 145 (57), 117 (12), and 115 (19).

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.73; H, 6.27.

In an experiment where 10 mmol of the ketone 19 was reduced with 20 mg-atom of Li in a mixture of 100 ml of NH_3 and 20 ml of Et_2O with no

added t-BuOH, 386 mg (27%) of the dihydro dimer 43, mp 182.2-185°, was isolated from the crude product by trituration with Et_2O. Although the residual product contained (glpc analysis) some tetralol (41) and tetralone (42) the bulk of the material separated by susequent chromatography was 734 mg of the crude dihydro dimer 43 (and/or its stereoisomer), mp 128-182°.

Preparation of an Authentic Sample of the Alcohol 41

A solution of 4.38 g (30 mmol) 1-tetralone (42) in 5 ml Et_2O was added dropwise during 5 min to a suspension of 0.61 g (16 mmol) $LiAlH_4$ in 20 ml Et_2O. After the mixture had been refluxed 30 min, the crude product was isolated and was found (glpc analysis) to contain starting ketone 42. The crude product was dissolved in 5 ml Et_2O and was added during 2 min to a suspension of 0.61 g (16 mmol) $LiAlH_4$ in 35 ml Et_2O. After the mixture had been stirred 4 hr at 25°, the product was isolated and was found (glpc analysis) to contain only 1-tetralol (41). Distillation separated 3.34 g (75%) of the alcohol 41 as a colorless liquid, bp 85.0-86.7° (0.35 mm), n^{25}_D 1.5620 - 1.5629 (lit.[25] bp 132-134° (12 mm), n^{20}_D 1.5672.

References and Notes

1. For examples, discussion, and other references, see H. O. House and K. A. J. Snoble, J. Org. Chem., 41, 3076 (1976).

2. H. O. House, A. V. Prabhu, J. M. Wilkins, and L. F. Lee, J. Org. Chem., 41, 3067 (1976).

3. (a) H. Shiota, K. Ohkata, and T. Hanafusa, Chem. Lett., 1153 (1974); (b) S. S. Hall, C. K. Sha, and F. Jordan, J. Org. Chem., 41, 1494 (1976).

4. L. Mandell, J. C. Johnson, and R. A. Day, Jr., J. Org. Chem., 43, 1616 (1978).

5. (a) H. O. House and C. B. Hudson, J. Org. Chem., 35, 647 (1970); (b) H. O. House, C. B. Hudson, and E. J. Racah, Ibid., 37, 989 (1972); (c) H. O. House and W. C. McDaniel, Ibid., 42, 2155 (1977).

6. (a) A. Burger and W. L. Yost, J. Am. Chem. Soc., 70, 2198 (1948); (b) E. N. Trachtenberg and G. Odian, Ibid., 80, 4015 (1958); (c) C. Dupin and R. Fraisse-Jullien, Bull. Soc. Chim. Fr., 1993 (1964); (d) R. Fraisse-Jullien and C. Frejaville, Ibid., 219 (1970).

7. (a) R. Jacquier and P. Besinet, Bull. Soc. Chim. Fr., 989 (1957); (b) G. R. Elling, R. C. Hahn, and G. Schwab, J. Am. Chem. Soc., 95, 5659 (1973).

8. (a) Reduction potentials were measured in this laboratory by R. F. Sieloff. Additional details can be found in a paper entitled "Perhydroindan Derivatives. 19. Opening of a Cyclopropyl Ketone that is Part of an Indanone System," by H. O. House, W. C. McDaniel, R. F. Sieloff, and D. Van Derveer, submitted to J. Org. Chem. (b) The x-ray diffraction study was performed in this laboratory by D. Van Derveer. Additional details can be found in the paper described in reference 8a.

9. H. O. House, Accts. Chem. Res., 9, 59 (1976).

10. R. Fraisse-Jullien and C. Frejaville, Bull. Soc. Chim. Fr., 4449 (1968).

11. (a) R. Fraisse-Jullien, C. Frejaville, V. Toure, and M. Derieux, Bull. Soc. Chim. Fr., 4444 (1968); (b) E. C. Friedrich, D. B. Taggart, and M. A. Saleh, J. Org. Chem., 42, 1437 (1977).

12. H. O. House and J. M. Wilkins, J. Org. Chem., 43, 0000 (1978).

13. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer, Model 257,

infrared recording spectrometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin-Elmer, Model 202, recording spectrometer. The proton nmr spectra were determined at 60 mHz with a Varian, Model A-60 or Model T-60-A, nmr spectrometer and the 13C nmr spectra were determined at 25 mHz with a JEOL Fourier transform spectormeter, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive intermediates were performed under a nitrogen atmosphere.

14. N. E. Searle, Org. Syntheses, Coll. Vol. 4, 424 (1963).

15. M. M. Fawzi and C. D. Gutsche, J. Org. Chem., 31, 1390 (1966).

16. J. v.Braun and A. Stuckenschmidt, Ber., 56, 1724 (1923).

17. H. Adkins and J. W. Davis, J. Am. Chem. Soc., 71, 2955 (1949).

18. H. O. House, D. J. Reif, and R. L. Wasson, J. Am. Chem. Soc., 79, 2490 (1957).

19. H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, J. Am. Chem. Soc., 82, 1452 (1960).

20. G. Gilbert and B. F. Aycock, J. Org. Chem., 22, 1013 (1957).

21. J. A. Barltrop, R. M. Acheson, P. G. Philpott, K. E. MacPhee, and J. S. Hunt, J. Chem. Soc., 2928 (1956).

22. W. J. Dale and H. E. Hennis, J. Am. Chem. Soc., 81, 2143 (1959).

23. H. E. Simmons and R. D. Smith, J. Am. Chem. Soc., 81, 4256 (1959).

24. R. Fuchs, C. A. Kaplan, J. J. Bloomfield, and L. F. Hatch, J. Org. Chem., 27, 733 (1962).

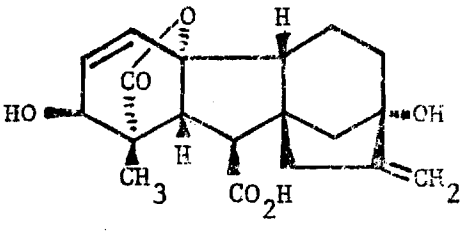
25. G. Baddeley, J. W. Rasburn, and R. Rose, J. Chem. Soc., 3168 (1968).

CHAPTER IV

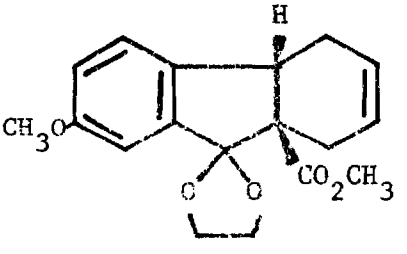
STUDIES ON THE SYNTHESIS OF GAMMA LACTONES

Discussion

In an earlier investigation of a possible precursor for gibberellic acid (1), the tetrahydrofluorene derivative 2 was prepared.[1] The work of House[2] has shown that the D ring of tetracyclic gibberellins can be synthesized thru the tetracyclic lactone 5 (Scheme I). Consequently, the first important step in the conversion of ester 2 into a molecule containing the D ring would be the formation of lactone 13 (Scheme II).



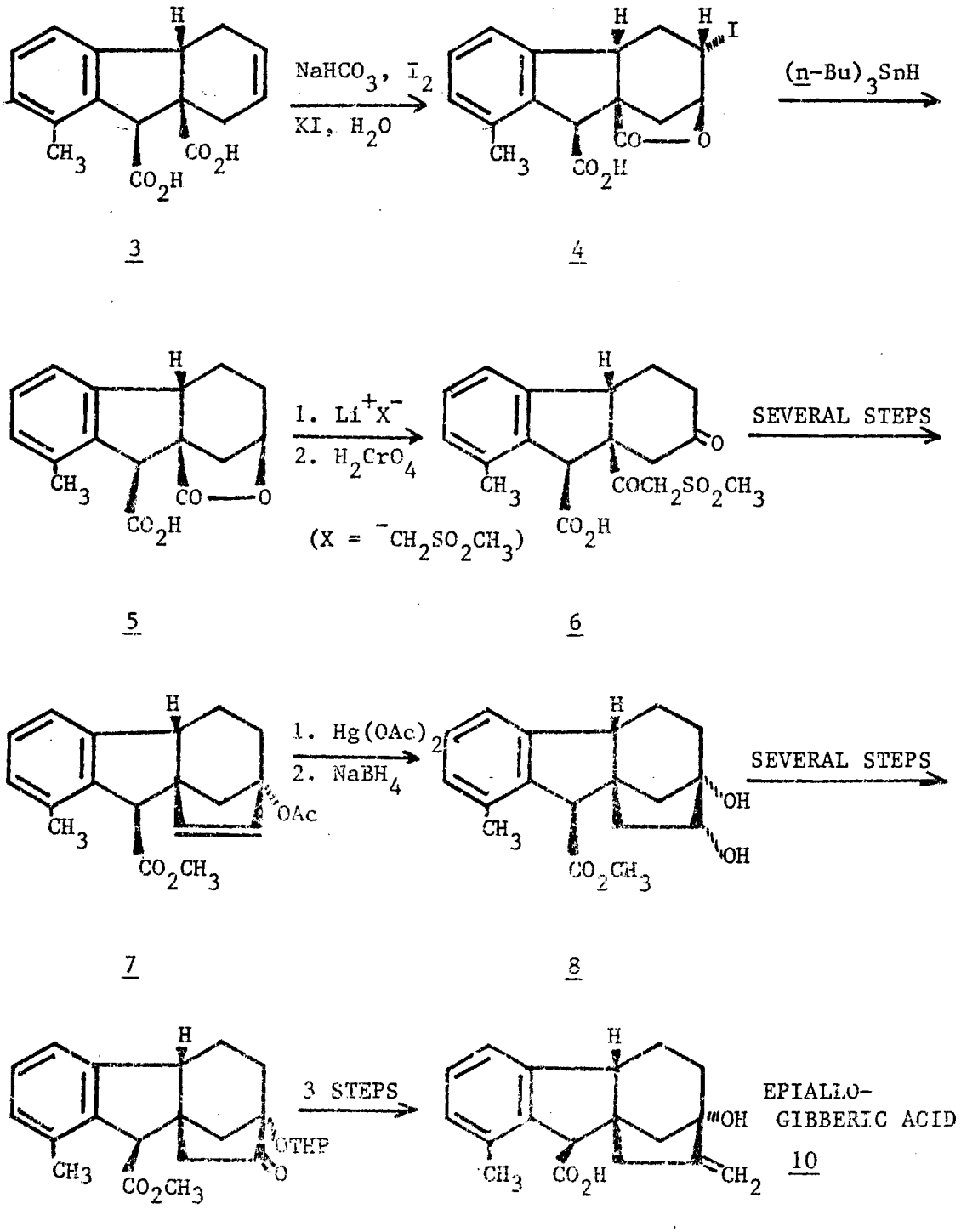
1



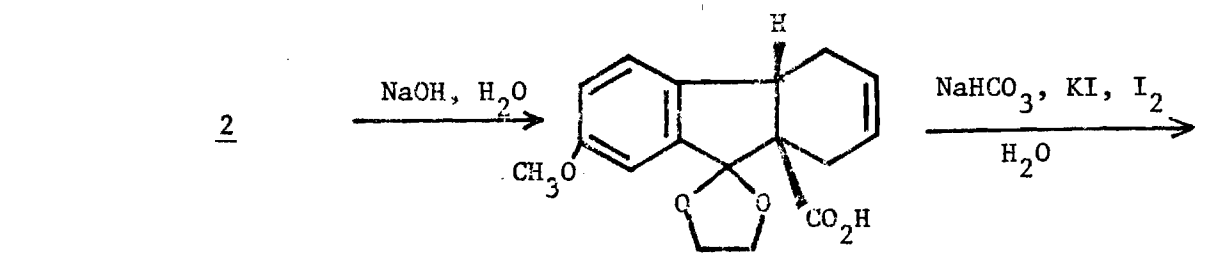
2

The ketal acid 11 was prepared in 96% yield by reaction of the ester 2 with refluxing aqueous NaOH in MeOH. The iodolactone 12 was then prepared in 79% yield by reacting the acid 11 with aqueous $NaHCO_3$ containing KI and iodine. Reduction of the iodolactone 12 with $(n\text{-}Bu)_3SnH$ in refluxing benzene yielded the lactone 13 in 61% overall yield from 2.

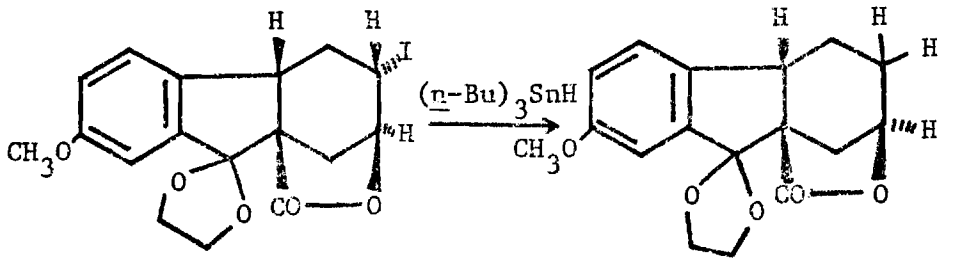
SCHEME I


NaHCO3, I2
KI, H2O
(n-Bu)3SnH
1. Li+X-
2. H2CrO4
(X = -CH2SO2CH3)
SEVERAL STEPS
1. Hg(OAc)2
2. NaBH4
SEVERAL STEPS
3 STEPS
EPIALLO-
GIBBERIC ACID
3
4
5
6
7
8
9
10

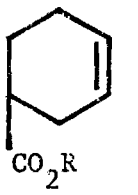
SCHEME II



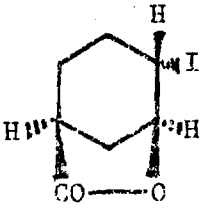
11



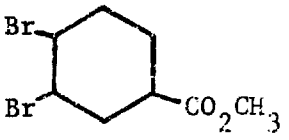
12 13



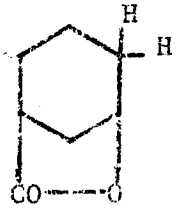
14, R = H
15, R = CH_3
16, R = $CH_2CH_2CO_2H$



17



19



18

The model ester 15 was prepared in two steps from acrylic acid. Reaction of butadiene with acrylic acid in an autoclave at 130° yielded acid 14 which was then esterfied using BF_3 in MeOH. If the acrylic acid was not purified prior to use the carboxylic acid 16 was also formed from the reaction of butadiene with acrylic acid dimer.

Ester 15 was then treated with various reagents in an attempt to effect formation of lactone 18. Reaction with Br_2 at 0° in Et_2O yielded only the dibromoester 19. Iodine in refluxing CCl_4 yielded mostly the starting ester 15 with no lactone detected (ir analysis). Reaction with $Hg(OAc)_2$ in aqueous THF yielded only recovered starting ester.

An authentic sample of the lactone 18 was prepared from the acid 14 by initial formation of the iodolactone 17 in 93% yield. Reduction of 17 with $(n\text{-}Bu)_3SnH$ and subsequent purification by successive distillation, chromatography, and sublimation, yielded 48% of the pure lactone 18.

Experimental Section[3]

A solution of 1.419 g (4.49 mmol) of the ester 2[1] and 25 ml of aqueous 4 M NaOH in 25 ml MeOH was refluxed for 24 hr and then diluted with 100 ml H_2O and extracted with Et_2O to separate 61 mg of neutral material. The aqueous phase was mixed with 200 g of ice and 500 ml CH_2Cl_2 and then acidified (pH 1) by the dropwise addition of cold aqueous 1 M HCl. The CH_2Cl_2 layer was separated immediately and the cold aqueous phase was extracted with an additional portion of CH_2Cl_2. After the combined CH_2Cl_2 solutions had been washed with aqueous NaCl, dried, and concentrated, a solution of the residue in warm $CHCl_3$ was diluted with hexane to precipitate 1.31 g (96%) of the ketal acid 11 as a pale-cream solid mp 137-137.8° dec. Recrystallization from either $CHCl_3$-hexane or THF-hexane afforded the acid 2 as small white plates, mp 138.5-140° dec; ir (CCl_4), 1733 and 1708 (shoulder) cm^{-1} (carboxyl C=O); uv max (95% EtOH), 213 nm (ε 6220), 221 nm (ε 6120), 226 nm (ε 5980), 283.5 nm (ε 2440), and 290 nm (ε 2150); nmr ($CDCl_3$), δ 11.32 (1H, broad, OH), 6.6-7.3 (3H, m, aryl CH), 5.67 (2H, broad, vinyl CH), 3.8-4.5 (5H, m, ketal CH_2 and benzylic CH), 3.78 (3H, s, OCH_3), and 1.8-3.0 (4H, m, CH_2); mass spectrum, m/e (rel. intensity), 302 (M^+, 8), 259 (18), 258 (100), 213 (57), 204 (17), 197 (25), 196 (59), and 195 (63).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.53; H, 6.05.

Preparation of the Iodolactone 3

The crude ketal acid 11 (4.04 g) obtained by the previously described saponification of 4.462 g (14.1 mmol) of the ester 2 was dissolved in a mixture of 8.40 g (100 mmol) of $NaHCO_3$, 25 ml H_2O, and

75 ml of THF, and then a mixture of 2.81 g (16.9 mmol) of KI, 10.74 g (42.3 mmol) of I_2, and 75 ml of H_2O was added. After the resulting mixture had been stirred (N_2 atmosphere) for 24 hr at 25°, it was partitioned between Et_2O and aqueous $Na_2S_2O_3$. The colorless Et_2O phase was washed with aqueous $NaHCO_3$, dried, and concentrated to leave 3.44 g of the crude iodolactone 12, mp 149.5-150° dec. Extraction of the various aqueous solutions with $CHCl_3$ separated an additional 1.31 g (total yield 4.75 g or 79%) of the crude iodolactone 12, mp 157-158°. The combined crude samples of the iodolactone were recrystallized from a $CHCl_3$-hexane mixture to give the pure iodolactone 12 as a colorless solid, mp 162.9-163.5° dec; ir ($CHCl_3$), 1777 cm^{-1} (γ-lactone C=O); uv max (95% EtOH), 220 nm (ϵ 9430), 225 nm (shoulder, 9340), 281 nm (ϵ 3040), and 288.5 nm (ϵ 2610); nmr ($CDCl_3$, δ 6.8-7.2 (3H, M, aryl CH), 5.07 (1H, d, J = 5 Hz, further splitting not resolved, CHO), 3.0-4.6 (9H, m, aliphatic CH including a CH_3O at 3.82), and 2.0-2.6 (4H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 428 (M^+, 16), 214 (64), 210 (47), 195 (22), 160 (100), 155 (84), and 44 (36).

Anal. Calcd for $C_{17}H_{17}IO_5$: C, 47.67; H, 4.00; I, 29.65. Found: C, 47.69; H, 4.03; I, 29.58.

Preparation of the Ketal Lactone 4

The previously described[4] reduction of $(n\text{-Bu})_3SnCl$ with $LiAlH_4$ in Et_2O yielded 82% of $(n\text{-Bu})_3SnH$ as a colorless liquid, bp 72-75° (0.2 mm), $n^{25}D$ 1.4707 (lit.[4] bp 76-81° (0.7-0.9 mm)). A slurry of 3.23 g (7.5 mmol) of the iodolactone 12 in a mixture of 2.41 g (8.28 mmol) of $(n\text{-Bu})_3SnH$, 30 ml of PhH, and 30 ml of Et_2O was stirred at 25° for 24 hr and then cooled to 0°. The supernatant liquid was decanted to leave 2.18 g of colorless solid containing (nmr analysis) ca. 75% of the lactone 13 and

ca. 25% of the iodolactone 12. This material was added to a solution of 1.103 g (3.8 mmol) of $(n\text{-Bu})_3SnH$ in 30 ml of Et_2O and 30 ml PhH and the resulting suspension was refluxed with stirring for an additional 24 hr. The resulting suspension was concentrated and the residual solid was washed thoroughly with hexane to leave 1.826 g (81%) of the lactone 13 as a colorless solid, mp 200.1-202°. Recrystallization from a $CHCl_3$-hexane mixture separated the lactone 13 as colorless prisms, mp 200.1-202°; ir ($CHCl_3$), 1770 cm^{-1} (γ-lactone C=O); uv max (95% EtOH), 220 nm (ϵ 6520), 282 nm (ϵ 2440), and 288.5 nm (ϵ 2220); nmr ($CDCl_3$), δ 6.7-7.4 (3H, m, aryl CH), 4.6-5.0 (1H, m, OCH), 3.9-4.4 (4H, m, ketal OCH_2), 3.82 (3H, s, OCH_3), 3.53 (1H, t, J = 7 Hz, benzylic CH), and 1.4-2.7 (6H, m, CH_2); mass spectrum, m/e (rel. intensity), 303 (22), 302 (M^+, 100), 258 (24), 214 (39), 213 (87), 187 (38), 174 (24), 173 (22), and 115 (23).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.52; H, 6.04.

Preparation of the Acid 5 and Ester 6

A mixture of 28.82 g (0.40 mol) of freshly distilled acrylic acid, 32 g (0.59 mol) of butadiene, 2.5 g (20 mmol) of p-methoxyphenol (an inhibitor), and 10 ml of PhH was warmed slowly during 1 hr to 100° and then heated to 120° in an autoclave for 7 hr, cooled, and partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The aqueous layer was acidified and extracted with Et_2O. After the ethereal layer had been dried and concentrated, distillation of the residue (62 g) separated 40.02 g (79%) of the acid 14, bp 85-90° (0.6 mm), $n^{25}D$ 1.4790 - 1.4794 (lit. bp 132.5-133° (20 mm),[5] 126° (16 mm),[6] $n^{20}D$ 1.4812,[5] $n^{25}D$ 1.4780[6]); ir (CCl_4), 2800-3400 (broad, assoc, OH) and 1705 cm^{-1} (carboxyl C=O); nmr (CCl_4),

δ 12.28 (1H, s, OH), 5.2-6.1 (2H, m, vinyl CH), and 1.2-2.9 (7H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 126 (M^+, 31), 108 (35), 81 (100), 80 (61), 79 (33), and 41 (21).

From a comparable reaction that employed undistilled commercial acrylic acid and no inhibitor, the yield of acid 14 (bp 85-90° (0.3 mm), $\underline{n}^{25}\underline{D}$ 1.4785) was only 27.9 g (55%) and 9.06 g of higher boiling fractions, bp 90-150° (0.3 mm), $\underline{n}^{25}\underline{D}$ 1.4768 - 1.4787. The spectra of this higher boiling material suggest that it is the ester acid 16; ir (CCl_4), 2600-3400 (broad, assoc. OH), 1735 (ester C=O), and 1716 cm^{-1} (carboxyl C=O); nmr (CCl_4), δ 11.22 (1H, s, OH), 5.6-5.8 (2H, m, vinyl CH), 4.33 (2H, t, J = 6 Hz, CH_2O), 2.68 (2H, t, J = 6 Hz, CH_2CO_2R), and 1.4-2.7 (7H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 198 (M^+, 2), 109 (11), 108 (19), 81 (44), 80 (100), 79 (28), 55 (15), and 41 (13). This by-product 16 arises from the known[7] acid, $CH_2{=}CHCO_2CH_2CH_2CO_2H$, present in crude acrylic acid. Thus, repeated fractional distillation of 100 g of commercial acrylic acid separated 10.3 g of the acid, $CH_2{=}CHCO_2CH_2CH_2CO_2H$, as a colorless liquid, bp 105-109° (0.1 mm), $\underline{n}^{25}\underline{D}$ 1.4528 (lit.[7] bp 136° (10mm), $\underline{n}^{20}\underline{D}$ 1.4522); ir (CCl_4), 2950 (broad, assoc. OH), 1720 (broad, C=O of ester and carboxylic acid), and 1638 cm^{-1} (C=C); nmr (CCl_4), δ 11.57 (1H, s, CH), 5.6-6.7 (3H, m, vinyl CH), 4.37 (2H, t, J = 6 Hz, OCH_2), and 2.70 (2H, t, J = 6 Hz, CH_2CO_2R); mass spectrum, m/e (rel. intensity), 89 (8), 73 (25), 56 (9), 55 (100), 45 (14), and 43 (10).

A solution of 18.92 g (0.150 mol) of the acid 14 and 25.55 g (0.180 mol) of Et_2O-BF_3 (freshly distilled) in 250 ml MeOH was allowed to stand at 25° for 12 hr. After the mixture had been partitioned between H_2O and Et_2O, the ethereal layer was washed with aqueous $NaHCO_3$, dried

and concentrated. Distillation of the residual liquid (20.9 g) separated 18.89 g (90%) of the ester 15, bp 74° (18 mm), $n^{25}D$ 1.4690 (lit.[5] bp 79.5° (20 mm), $n^{20}D$ 1.4650); ir (CCl_4), 1740 cm^{-1} (ester C=O); nmr (CCl_4), δ 5.6-5.8 (2H, m, vinyl CH), 3.67 (3H, s, OCH_3), and 1.4-2.7 (7H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 140 (M^+, 28), 109 (20), 108 (48), 81 (100), 80 (96), and 79 (39).

Preparation of the Iodolactone 8

A solution prepared from 9.46 g (75 mmol) of the acid 14, 31.5 g (375 mmol) of $NaHCO_3$, and 750 ml of H_2O was treated with a mixture of 57.1 g (225 mmol) of I_2, 14.5 g (87 mmol) of KI, and 375 ml of H_2O. After the resulting suspension had been stirred at 25° for 4 hr, it was partitioned between aqueous $Na_2S_2O_3$ and Et_2O. The ethereal layer was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated to leave 17.66 g (93%) of the lactone 17 as a white solid, mp 132.8-135° dec. Recrystallization from a $CHCl_3$-hexane mixture separated 14.37 g of the lactone 17 as a white powder, mp 133.2-135.9° dec (lit.[8] mp 134° dec); ir (CCl_4), 1805 and 1790 cm^{-1} (γ-lactone C=O); nmr (CCl_4), δ 4.7-5.0 (1H, m, OCH), 4.4-4.7 (1H, m, CHI), and 1.6-3.0 (7H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 252 (M^+, 12), 154 (35), 128 (20), 127 (45), 125 (94), 97 (24), 83 (26), 81 (100), 80 (21), 79 (58), 77 (22), 67 (21), 55 (22), 41 (43), and 39 (34).

Preparation of the Lactone 9

A solution of 6.30 g (25 mmol) of the iodolactone 17 in 100 ml Et_2O was treated with 8.824 g (30.3 mmol) of $(n\text{-}Bu)_3SnH$ and the resulting solution was stirred at 25° for 24 hr and then concentrated. The residual liquid (15.57 g) was distilled under reduced pressure in a

short-path still to separate 5.70 g of colorless semi-solid containing (nmr analysis) the crude lactone 18. This distillate was chromatographed on silica gel with an EtOAc-hexane eluent (3:17 v/v) to separate early fractions containing organotin compounds and later fractions containing 1.54 g of the lactone 18 as a waxy solid. Sublimation (100° at 0.1 mm) separated 1.50 g (48%) of the lactone 18 as a colorless solid, mp 109-117.8°. Recrystallization from hexane afforded the pure lactone 18, mp 121.8-122.9° (lit.[9] mp 120-121.5°); ir (CCl_4), 1784 cm^{-1} (γ-lactone C=O); ^1H nmr (CCl_4), δ 4.5-4.9 (1H, m, OCH_2), and 0.9-2.7 (9H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 126 (M^+, 4), 84 (96), 83 (42), 82 (62), 70 (51), 67 (100), 55 (46), 54 (87), 42 (36), 41 (76), and 39 (46); ^{13}C nmr ($CDCl_3$, multiplicity in off-resonance decoupling), 178.1 (s), 77.5 (d), 38.8 (d), 37.4 (t), 27.9 (t), 26.3 (t), and 18.4 (t) ppm.

Attempts to form the lactone 9 From the Unsaturated Ester 6. A. With $Hg(OAc)_2$

After a mixture (initially a suspension) of 7.01 g (50 mmol) of the ester 15 and 15.93 g (50 mmol) of $Hg(OAc)_2$ in 100 ml of THF and 50 ml of H_2O had been stirred at 25° for 13 hr, the resulting solution was partitioned between CH_2Cl_2 and aqueous NaCl. After the organic phase had been washed with aqueous $NaHCO_3$ and concentrated, a solution of the residual liquid (15.1 g) in 350 ml of i-PrOH was treated with 3.78 g (100 mmol) of $NaBH_4$. The resulting gray suspension was stirred at 25° for 45 min and then partitioned between H_2O and $CHCl_3$. The organic phase was dried, concentrated, and distilled to separate 5.15 g (73%) of the crude unchanged ester 15, bp 80° (15 mm), $n^{25}D$ 1.4575 - 1.4576, and 0.396 g of a fraction containing a mixture of the starting ester 15 and an

unidentified alcohol. Similar experiments with other reaction solvents also failed to yield an appreciable quantity of the lactone 18.

Attempts to form the Lactone 9 From the Unsaturated Ester 6. B. With Br_2

To a cold (0°) solution of 0.42 g (3.0 mmol) of the ester 15 in 50 ml of CCl_4 was added, dropwise with stirring during 5 min, a solution of 0.48 g (3.0 mmol) of Br_2 in 10 ml of CCl_4. The resulting colorless solution exhibited ir absorption corresponding to an ester (1732 cm^{-1}) but not a γ-lactone. After the mixture had been partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was washed with aqueous NaCl, dried, concentrated, and distilled in a short-path still (150° at 0.1 mm) to separate 802 mg (89%) of the dibromo ester 19 (probably a mixture of stereoisomers) as a colorless liquid, $n^{25}D$ 1.5369 (lit.[10] bp 85-86° (0.1 mm), $n^{25}D$ 1.5375); ir (CCl_4), 1735 cm^{-1} (ester C=O); nmr (CCl_4), δ 4.4-4.9 (2H, m, BrCH), 3.65 (3H, s, OCH_3), and 1.6-3.3 (7H, m, aliphatic CH); mass spectrum, m/e (rel. intensity), 271 (2), 269 (4), 267 (2), 221 (20), 219 (20), 139 (100), 121 (20), 107 (19), 81 (30), and 80 (30). A similar attempt to form the lactone 18 by reaction with I_2 in CCl_4[11] resulted in partial recovery of the starting material and the formation of high-molecular materials that lacked ir absorption corresponding to lactone 18.

References and Notes

1. H. O. House and W. C. McDaniel, J. Org. Chem., 42, 2155 (1977).

2. (a) H. O. House, D. G. Melillo, and F. J. Sauter, J. Org. Chem., 38, 741 (1973); (b) H. O. House and D. G. Melillo, J. Org. Chem., 38, 1398 (1973).

3. All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary, Model 14, or a Perkin-Elmer, Model 202, recording spectrophotometer. The proton nmr spectra were determined at 60 mHz with a Varian, Model A-60 or Model T-60-A, nmr spectrometer and the 13C nmr spectra were determined at 25 mHz with a JEOL Fourier transform spectrometer, Model FFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7, or a Varian, Model M-66, mass spectrometer. All reactions involving strong bases or reactive intermediates were performed under a nitrogen atmosphere.

4. G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, J. Appl. Chem., 7, 366 (1957).

5. A. A. Petrov and N. P. Sopov, J. Gen. Chem., USSR, 17, 2228 (1947); Chem. Abstr., 42, 4957 (1948).

6. F. X. Werber, J. E. Jansen, and T. L. Gresham, J. Am. Chem. Soc., 74, 532 (1952).

7. S. M. Sherlin, A. Ya. Berlin, T. A. Serebrennikova, and F. E. Rabinovich, J. Gen. Chem., USSR, 8, 22 (1938); Chem. Abstr., 32, 5398 (1938).

8. R. Grewe, A. Heinke, and C. Sommer, Chem. Ber., 89, 1978 (1956).

9. H. O. House, H. Babad, R. B. Toothill, and A. W. Noltes, J. Org. Chem., 27, 4141 (1962).

10. P. L. Barili, G. Bellucci, G. Berti, F. Marioni, A. Marsili, and I. Morelli, J. Chem. Soc., Perkin II, 53 (1972).

11. See H. J. Gunther and V. Jager, Tetrahedron Lett., 2539 (1977).

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